

**Benefits and harms of testosterone replacement therapy
in hypogonadal men:
A systematic review and network meta-analysis**

JESSE ELLIOTT

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of
the requirements for Master of Science degree in the School of Epidemiology, Public Health
and Preventive Medicine

School of Epidemiology, Public Health and Preventive Medicine

Faculty of Medicine

University of Ottawa

ABSTRACT

Testosterone products comprise a multi-billion dollar industry; however, Health Canada and the United States Food and Drug Administration have issued statements of concern about their safety, and their benefits are unclear. In the first phase of this study, we performed a systematic review of the current evidence for the benefits of testosterone replacement therapy. In the second phase, we analyzed the evidence from randomized controlled trials for the benefits of testosterone replacement therapy (depression, quality of life, erectile function, libido, total testosterone level). In the third phase, we analyzed data for harms (cardiovascular death, myocardial infarction, stroke, newly diagnosed prostate cancer, coronary artery disease or diabetes, serious adverse events, withdrawals due to adverse events, erythrocytosis) from randomized controlled trials and non-randomized studies. In general, most included studies had a short duration and were poorly reported. Additional high-quality research into the long-term safety of testosterone products is needed.

EXECUTIVE SUMMARY

Background: Despite its widespread use, the efficacy of testosterone in improving depression, quality of life, libido, and erectile function is not well established. We evaluated the current evidence of the benefits and harms associated with testosterone replacement therapy in a systematic review and network meta-analysis.

Methods: We performed a systematic review and network meta-analysis of randomized controlled trials and non-randomized studies of interventions of at least 3 months' duration. Eligible studies were located through an electronic search of MEDLINE, Embase, and Cochrane CENTRAL. Studies that included adult men (≥ 18 yr) with low testosterone (serum total testosterone ≤ 12 nmol/L) were included. The efficacy outcomes of interest were depression, quality of life, libido, erectile function, and total testosterone level. The harm outcomes of interest were cardiovascular death, myocardial infarction, stroke, newly diagnosed disease (prostate cancer, diabetes, cardiovascular disease), erythrocytosis, withdrawals due to adverse events, and serious adverse events. Data from randomized controlled trials were included for efficacy outcomes, and data from randomized and non-randomized studies were included for harm outcomes. Mean differences and standardized mean differences with standard deviations were calculated for continuous data, and odds ratios with 95% credible intervals were calculated for dichotomous data. Subgroup analyses included route of administration, duration of treatment, participant age, and comorbidities. Risk of bias and publication bias were assessed.

Results: Seventy RCTs and 38 nonrandomized studies met the inclusion criteria. The included studies were mostly shorter than 1-year duration and were generally poorly reported and of high or unclear risk of bias. Compared with placebo, 3 (of 10) testosterone products improved depression and 1 (of 14) improved quality of life. There were no significant differences between placebo and any testosterone product for libido or erectile function. Six (of 15) products increased testosterone levels at 3 months, 8 (of 17) increased levels at 6 months, and 11/25 increased levels at end of study. In head-to-head comparisons, oral testosterone undecanoate improved symptoms of depression relative to the other testosterone products. There were no differences among testosterone products for quality of life, erectile

function, or libido. When only studies at low risk of bias were considered, there were no significant differences between placebo and any testosterone treatment for depression, erectile function, and libido. Among studies at low risk of bias, testosterone patch (5 mg/d) was associated with significantly improved quality of life relative to placebo, 1% testosterone gel (50 mg/d), and oral testosterone undecanoate (160 mg/d). When only studies that reported having no industry funding were considered, there were no significant differences between any testosterone replacement therapy and placebo or among the treatments for depression, quality of life, erectile function, or libido.

We found no increased risk of cardiovascular death, myocardial infarction, or serious adverse events. Oral testosterone undecanoate was associated with lower odds of prostate cancer compared with testosterone patch or intramuscular enanthate; however, there were no significant differences after correction for zero events. Testosterone 1.62% gel was associated with significantly more withdrawals due to adverse events compared with placebo, 1% testosterone gel, and intramuscular testosterone enanthate, and testosterone patch had higher odds of withdrawals due to adverse events compared with intramuscular testosterone undecanoate. There were limited data for stroke; however, in a pairwise meta-analysis, we found no increased risk of stroke for testosterone compared with placebo.

The included non-randomized studies were generally poorly reported and of poor quality. Of the 38 included studies, 26 studies did not report an outcome of interest. The most frequently reported safety outcome was prostate cancer.

Interpretation: The use of some, but not all, testosterone products resolved symptoms of depression and improved quality of life among men with low testosterone; however, these findings were generally from studies at high or unclear risk of bias. No product was effective for improving erectile function or libido. There was no increased risk of cardiovascular death, myocardial infarction, or serious adverse events among participants who used testosterone replacement therapy. The odds of prostate cancer and withdrawals due to adverse events may vary by testosterone product. The quality of the included studies was generally low, and further long-term high-quality studies are needed to clarify the benefits and harms of testosterone replacement therapy in this population.

ACKNOWLEDGEMENTS

I would like to thank Dr. George Wells for his invaluable guidance and direction on this project and beyond. I would also like to thank my colleagues, Joan Peterson, Ahmed Kotb, and Amy Johnston, who assisted with screening of records and data extraction. Thank you to Lily Chen for assistance and guidance with statistical analysis. Thank you to Shuching Hsieh for many, many discussions about risk of bias.

I would also like to thank Joe and Zack Elliott for their support and understanding.

Thank you to Dr. John Fletcher for encouraging me to always think about “the next step.”

Funding for this project was received from the Ontario Drug Policy Research Network. Jesse was supported by a University of Ottawa Graduate Entrance Scholarship and a Department of Epidemiology Recruitment Scholarship.

TABLE OF CONTENTS

ABSTRACT	ii
EXECUTIVE SUMMARY.....	iii
ACKNOWLEDGEMENTS.....	v
TABLE OF CONTENTS.....	vi
TABLE OF TABLES	x
TABLE OF FIGURES	xv
CHAPTER 1: INTRODUCTION	1
1.1 RATIONALE.....	1
1.2 WHY IS A REVIEW NEEDED NOW?	2
1.3 OBJECTIVES	2
1.4 RESEARCH QUESTIONS	2
1.5 OUTLINE.....	2
1.6 REFERENCES	3
CHAPTER 2: BACKGROUND	4
2.1 HYPOGONADISM	4
2.2 DIAGNOSIS OF HYPOGONADISM.....	5
2.3 EPIDEMIOLOGY	6
2.4 TESTOSTERONE REPLACEMENT THERAPY	8
2.5 CLINICAL PRACTICE GUIDELINES.....	9
2.6 WHAT IS CURRENTLY KNOWN	10
2.6.1 BENEFITS.....	10
2.6.2 HARMS	11
2.7 WHY IS A REVIEW NEEDED NOW?	14
2.8 REFERENCES	15
CHAPTER 3: BENEFITS OF TESTOSTERONE REPLACEMENT THERAPY AMONG HYPOGONADAL MEN	19
3.1 INTRODUCTION	19
3.2 METHODS.....	20
3.2.1 SEARCH STRATEGY.....	20
3.2.2 STUDY SELECTION	21

3.2.3 OUTCOMES	22
3.2.4 DATA EXTRACTION	22
3.2.5 RISK OF BIAS.....	22
3.2.6 PUBLICATION BIAS.....	23
3.2.7 STATISTICAL ANALYSIS	23
3.2.8 SENSITIVITY ANALYSIS	25
3.2.9 SUBGROUP ANALYSIS.....	25
3.3 RESULTS	26
3.3.1 CHARACTERISTICS OF THE INCLUDED TRIALS.....	26
3.3.2 RISK OF BIAS.....	35
3.3.3 NETWORK META-ANALYSIS.....	37
DEPRESSION	38
QUALITY OF LIFE.....	47
ERECTILE FUNCTION.....	57
LIBIDO	66
TESTOSTERONE LEVELS	75
3.3.4 SUBGROUP ANALYSIS.....	87
ROUTE OF ADMINISTRATION	87
TREATMENT DURATION	95
AGE	106
COMORBIDITIES	118
3.4 DISCUSSION.....	124
3.4.1 SUMMARY.....	124
3.4.2 CONTEXT	125
DEPRESSION	125
QUALITY OF LIFE.....	127
ERECTILE FUNCTION.....	128
LIBIDO	129
3.4.3 INFLUENCE OF INDUSTRY FUNDING	131
3.4.4 Publication bias.....	132
3.4.5 INFLUENCE OF RISK OF BIAS	132
3.4.6 STRENGTHS AND LIMITATIONS	133
3.4.7 CONCLUSION	134
3.5 REFERENCES	135

CHAPTER 4: HARMS ASSOCIATED WITH THE USE OF TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL MEN	141
4.1 INTRODUCTION	141
4.2 METHODS.....	142
4.2.1 SEARCH STRATEGY.....	143
4.2.2 STUDY SELECTION	143
4.2.3 DATA EXTRACTION AND QUALITY ASSESSMENT.....	144
4.2.4 OUTCOMES	144
4.2.5 PUBLICATION BIAS.....	145
4.2.6 STATISTICAL ANALYSIS	145
META-ANALYSIS.....	145
NETWORK META-ANALYSIS	145
4.2.7 SENSITIVITY ANALYSIS	146
4.2.8 SUBGROUP ANALYSIS.....	147
4.3 RESULTS	148
4.3.1 CHARACTERISTICS OF THE INCLUDED STUDIES	148
4.3.2 RISK OF BIAS.....	152
RANDOMIZED CONTROLLED TRIALS	152
NON-RANDOMIZED INTERVENTIONAL STUDIES	152
4.3.4 EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS	154
CARDIOVASCULAR DEATH	155
MYOCARDIAL INFARCTION	160
STROKE	165
PROSTATE CANCER	167
SERIOUS ADVERSE EVENTS	172
WITHDRAWALS DUE TO ADVERSE EVENTS	177
ERYTHROCYTOSIS	188
DIABETES	188
SUBGROUP ANALYSES	191
4.3.5 EVIDENCE FROM NON-RANDOMIZED INTERVENTIONAL STUDIES	231
CARDIOVASCULAR DEATH	233
MYOCARDIAL INFARCTION	234
STROKE	235
PROSTATE CANCER	235

SERIOUS ADVERSE EVENTS	236
WITHDRAWALS DUE TO ADVERSE EVENTS	237
DIABETES	237
HEART DISEASE	237
ERYTHROCYTOSIS	237
SKIN REACTIONS.....	237
4.4 DISCUSSION.....	239
4.4.1 SUMMARY.....	239
4.4.2 CONTEXT	239
CARDIOVASCULAR DEATH	240
MYOCARDIAL INFARCTION	241
STROKE	241
PROSTATE CANCER	242
SERIOUS ADVERSE EVENTS	243
4.4.3 INFLUENCE OF INDUSTRY FUNDING	244
4.4.4 PUBLICATION BIAS.....	245
4.4.5 INFLUENCE OF RISK OF BIAS	246
4.4.6 STRENGTHS AND LIMITATIONS	246
4.4.7 CONCLUSION	247
4.5 REFERENCES	248
 CHAPTER 5: SUMMARY AND FUTURE DIRECTIONS	 256
5.1 SUMMARY.....	256
5.2 CLINICAL IMPORTANCE.....	259
5.2.1 Depression	259
5.2.2 Quality of life	261
5.2.3 Erectile function.....	262
5.2.4 Libido	262
5.3 FUTURE DIRECTIONS	262
5.4 IMPLICATIONS FOR PRACTICE	263
5.4 REFERENCES	264
 APPENDIX 1: DETAILED LITERATURE SEARCH STRATEGY	 265
APPENDIX 2: LIST OF INCLUDED STUDIES (RANDOMIZED AND NON-RANDOMIZED).....	269

APPENDIX 3: LIST OF RECORDS EXCLUDED AT FULL-TEXT REVIEW	275
APPENDIX 4: LIST OF CONFERENCE ABSTRACTS	304
APPENDIX 5: RISK OF BIAS ASSESSMENT OF RANDOMIZED CONTROLLED TRIALS.....	324
APPENDIX 6: EVALUATION OF NETWORK CONSISTENCY	357
APPENDIX 7: INCLUDED NON-RANDOMIZED STUDIES OF INTERVENTIONS	363
APPENDIX 8: ODDS RATIO, RELATIVE RISK, AND RISK DIFFERENCE FOR HARMS OUTCOMES	365
APPENDIX 9: COMPARISON OF ODDS RATIOS FOR HARMS OUTCOMES UNDER THE RANDOM- AND FIXED-EFFECTS MODELS	396

TABLE OF TABLES

CHAPTER 2

TABLE 2.1: SIGNS AND SYMPTOMS SUGGESTIVE OF ANDROGEN DEFICIENCY IN MEN	6
TABLE 2.2: GUIDELINES FOR THE DIAGNOSIS OF HYPOGONADISM IN MEN.....	7
TABLE 2.3: CHARACTERISTICS OF TESTOSTERONE REPLACEMENT PRODUCTS (26).....	9
TABLE 2.4: CHARACTERISTICS OF SYSTEMATIC REVIEWS EVALUATING HARMS ASSOCIATED WITH TESTOSTERONE REPLACEMENT THERAPY	13

CHAPTER 3

TABLE 3.1: CHARACTERISTICS OF INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST	28
TABLE 3.2: SUMMARY OF RANDOMIZED CONTROLLED TRIAL CHARACTERISTICS.....	35
TABLE 3.3: RISK OF BIAS OF INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST	36
TABLE 3.4: SUMMARY OF CHARACTERISTICS FOR EACH EVIDENCE NETWORK.....	38
TABLE 3.5: CHARACTERISTICS OF TRIALS THAT ASSESSED DEPRESSION.....	40
TABLE 3.6: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES	42
TABLE 3.7: DEPRESSION — HEAD-TO-HEAD COMPARISON OF THE TESTOSTERONE REPLACEMENT THERAPIES (VISUAL REPRESENTATION).....	42
TABLE 3.8: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR DEPRESSION	43
TABLE 3.9: DEPRESSION— HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS THAT REPORTED NO INDUSTRY FUNDING.....	46
TABLE 3.10: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED DEPRESSION	47
TABLE 3.11: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS.....	47
TABLE 3.12: CHARACTERISTICS OF TRIALS THAT ASSESSED QUALITY OF LIFE.....	50

TABLE 3.13: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES	52
TABLE 3.14: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR QUALITY OF LIFE	53
TABLE 3.15: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS THAT REPORTED NO INDUSTRY FUNDING	56
TABLE 3.16: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED QUALITY OF LIFE.....	57
TABLE 3.17: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS	58
TABLE 3.18: CHARACTERISTICS OF TRIALS THAT ASSESSED ERECTILE FUNCTION.....	59
TABLE 3.19: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES	62
TABLE 3.20: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR ERECTILE FUNCTION	62
TABLE 3.21: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS WITH THAT REPORTED HAVING NO INDUSTRY FUNDING	65
TABLE 3.22: RISK OF BIAS ASSESSMENT OF TRIALS THAT ASSESSED ERECTILE FUNCTION	66
TABLE 3.23: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS	66
TABLE 3.24: CHARACTERISTICS OF TRIALS THAT ASSESSED LIBIDO	68
TABLE 3.25: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES.....	70
TABLE 3.26: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR THE EFFECT OF TESTOSTERONE REPLACEMENT THERAPIES ON LIBIDO.....	70
TABLE 3.27: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS WITH THAT REPORTED HAVING NO INDUSTRY FUNDING.....	73
TABLE 3.28: RISK OF BIAS ASSESSMENT OF TRIALS THAT ASSESSED LIBIDO.....	74
TABLE 3.29: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS.....	74
TABLE 3.30: TOTAL TESTOSTERONE LEVEL, 3 MONTHS —MEAN DIFFERENCE (STANDARD DEVIATION).....	77
TABLE 3.31: TOTAL TESTOSTERONE LEVEL, 3 MONTHS — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES	78
TABLE 3.32: TOTAL TESTOSTERONE LEVEL, 6 MONTHS —MEAN DIFFERENCE (STANDARD DEVIATION).....	81
TABLE 3.33: TOTAL TESTOSTERONE LEVEL, 6 MONTHS — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES	82
TABLE 3.34: TOTAL TESTOSTERONE LEVEL, END OF TREATMENT —MEAN DIFFERENCE (STANDARD DEVIATION)	84
TABLE 3.35: HEAD-TO-HEAD COMPARISONS OF THE TESTOSTERONE REPLACEMENT THERAPIES AT END OF TREATMENT, TOTAL TESTOSTERONE LEVEL	86
TABLE 3.36: DEPRESSION — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION.....	88

TABLE 3.37: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION	90
TABLE 3.38: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE THERAPIES PRODUCTS, BY ROUTE OF ADMINISTRATION	91
TABLE 3.39: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION.....	92
TABLE 3.40: TOTAL TESTOSTERONE LEVEL, END OF TREATMENT — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION	94
TABLE 3.41: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS.....	96
TABLE 3.42: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS OR LONGER.....	97
TABLE 3.43: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS	99
TABLE 3.44: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS OR LONGER	100
TABLE 3.45: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS	102
TABLE 3.46: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS AND LONGER.....	102
TABLE 3.47: LIBIDO — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS.....	105
TABLE 3.48: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS AND LONGER	106
TABLE 3.49: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS	108
TABLE 3.50: CHARACTERISTICS OF TRIALS THAT ASSESSED DEPRESSION, BY AGE	109
TABLE 3.51: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS	110
TABLE 3.52: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED 65 YEARS AND OLDER.....	111
TABLE 3.53: CHARACTERISTICS OF TRIALS THAT ASSESSED QUALITY OF LIFE, BY AGE	112
TABLE 3.54: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS	113
TABLE 3.55: CHARACTERISTICS OF TRIALS THAT ASSESSED ERECTILE FUNCTION, BY AGE	114
TABLE 3.56: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG MEN AGED LESS THAN 65 YEARS.....	116
TABLE 3.57: CHARACTERISTICS OF TRIALS THAT ASSESSED LIBIDO, BY AGE.....	117

TABLE 3.58: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS OR METABOLIC SYNDROME	120
TABLE 3.59: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH DEPRESSION	121
TABLE 3.60: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH OBESITY	122
TABLE 3.61: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH CORONARY ARTERY DISEASE	123

CHAPTER 4

TABLE 4.1: CHARACTERISTICS OF INCLUDED NON-RANDOMIZED INTERVENTIONAL STUDIES	150
TABLE 4.2: SIGN50 ASSESSMENT OF NON-RANDOMIZED STUDIES	153
TABLE 4.3: SUMMARY OF OUTCOMES BY ANALYSIS METHOD	154
TABLE 4.4: SUMMARY OF NETWORK CHARACTERISTICS	155
TABLE 4.5: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL)	158
TABLE 4.6: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	158
TABLE 4.7: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED	159
TABLE 4.8: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL)	162
TABLE 4.9: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	163
TABLE 4.10: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED	163
TABLE 4.11: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL)	169
TABLE 4.12: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	170
TABLE 4.13: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED	170
TABLE 4.14: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL)	174
TABLE 4.15: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	175
TABLE 4.16: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED	175
TABLE 4.17: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL)	181
TABLE 4.18: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	183
TABLE 4.19: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED	185
TABLE 4.20: REPORTED SKIN REACTIONS IN RANDOMIZED CONTROLLED TRIALS	189

TABLE 4.21: CARDIOVASCULAR DEATH, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)	193
TABLE 4.22: CARDIOVASCULAR DEATH, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	193
TABLE 4.23: MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)	194
TABLE 4.24: MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	194
TABLE 4.25: PROSTATE CANCER, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)	196
TABLE 4.26: PROSTATE CANCER, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	196
TABLE 4.27: SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)	197
TABLE 4.28: SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	198
TABLE 4.29: WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), BY ROUTE	199
TABLE 4.30: WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	200
TABLE 4.31: CARDIOVASCULAR DEATH, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION	202
TABLE 4.32: PROSTATE CANCER, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)	205
TABLE 4.33: SERIOUS ADVERSE EVENTS, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)	207
TABLE 4.34: WITHDRAWALS DUE TO ADVERSE EVENTS, TREATMENT DURATION LESS THAN 6 MONTHS — ODDS RATIO (95% CREDIBLE INTERVAL)	209
TABLE 4.35: WITHDRAWALS DUE TO ADVERSE EVENTS, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)	211
TABLE 4.36: CHARACTERISTICS OF TRIALS THAT REPORTED CARDIOVASCULAR DEATH, BY AGE	213
TABLE 4.37: CHARACTERISTICS OF TRIALS THAT REPORTED MYOCARDIAL INFARCTION, BY AGE	215
TABLE 4.38: CHARACTERISTICS OF TRIALS THAT REPORTED STROKE, BY AGE	216
TABLE 4.39: CHARACTERISTICS OF TRIALS THAT REPORTED PROSTATE CANCER, BY AGE	217
TABLE 4.40: CHARACTERISTICS OF TRIALS THAT REPORTED SERIOUS ADVERSE EVENTS, BY AGE	219
TABLE 4.41: SERIOUS ADVERSE EVENTS, AGE 65 YEARS AND OLDER — ODDS RATIO (95% CREDIBLE INTERVAL)	222

TABLE 4.42: CHARACTERISTICS OF TRIALS THAT REPORTED WITHDRAWALS DUE TO ADVERSE EVENTS, BY AGE	222
TABLE 4.43: WITHDRAWALS DUE TO ADVERSE EVENTS, AGE LESS THAN 65 YEARS — ODDS RATIO (95% CREDIBLE INTERVAL)	224
TABLE 4.44: WITHDRAWALS DUE TO ADVERSE EVENTS, AGE 65 YEARS AND OLDER— ODDS RATIO (95% CREDIBLE INTERVAL)	226
TABLE 4.45: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS OR METABOLIC SYNDROME	228
TABLE 4.46: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH DEPRESSION	229
TABLE 4.47: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH OBESITY	229
TABLE 4.48: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH CORONARY ARTERY DISEASE	230
TABLE 4.49: OUTCOMES REPORTED IN NON-RANDOMIZED STUDIES	231
TABLE 4.50: COMPARISON OF HARM OUTCOMES AMONG ALL TRIALS, THOSE WITHOUT INDUSTRY FUNDING, AND THOSE AT LOW RISK OF BIAS	245

CHAPTER 5

TABLE 5.1: SUMMARY OF MAIN FINDINGS	257
TABLE 5.2: COMPARISON OF STATISTICAL SIGNIFICANCE AND CLINICAL IMPORTANCE	261

TABLE OF FIGURES

CHAPTER 2

FIGURE 2.1: CAUSES OF REDUCED ANDROGEN LEVELS IN MEN	4

CHAPTER 3

FIGURE 3.1: SELECTION OF STUDIES FOR INCLUSION IN THE SYSTEMATIC REVIEW (PRISMA)	27
FIGURE 3.2: RISK OF BIAS SUMMARY FOR INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST	36
FIGURE 3.3: EVIDENCE NETWORK FOR DEPRESSION	39
FIGURE 3.4: DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF TESTOSTERONE REPLACEMENT THERAPY ON DEPRESSIVE SYMPTOMS	44
FIGURE 3.5: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — DEPRESSION	45
FIGURE 3.6: EVIDENCE NETWORK FOR QUALITY OF LIFE	49
FIGURE 3.7: DIRECT EVIDENCE FOR QUALITY OF LIFE	54
FIGURE 3.8: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — QUALITY OF LIFE	55

FIGURE 3.9: EVIDENCE NETWORK FOR ERECTILE FUNCTION	61
FIGURE 3.10: DIRECT EVIDENCE FOR ERECTILE FUNCTION	63
FIGURE 3.11: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — ERECTILE FUNCTION	64
FIGURE 3.12: EVIDENCE NETWORK FOR LIBIDO	67
FIGURE 3.13: DIRECT EVIDENCE FOR LIBIDO	71
FIGURE 3.14: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — LIBIDO	72
FIGURE 3.15: EVIDENCE NETWORK DIAGRAM FOR TOTAL TESTOSTERONE LEVEL AFTER 3 MONTHS OF TREATMENT	75
FIGURE 3.16: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL AFTER 6 MONTHS OF TREATMENT	79
FIGURE 3.17: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL AT END OF TREATMENT.....	83
FIGURE 3.18: EVIDENCE NETWORK FOR DEPRESSION BY ROUTE OF ADMINISTRATION	88
FIGURE 3.19: EVIDENCE NETWORK FOR QUALITY OF LIFE, BY ROUTE OF ADMINISTRATION.....	89
FIGURE 3.20: EVIDENCE NETWORK FOR ERECTILE FUNCTION, BY ROUTE OF ADMINISTRATION.....	91
FIGURE 3.21: EVIDENCE NETWORK FOR LIBIDO, BY ROUTE OF ADMINISTRATION.....	92
FIGURE 3.22: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL, END OF TREATMENT, ROUTE OF ADMISTRATION.....	94
FIGURE 3.23: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS WITH A TREATMENT DURATION OF LESS THAN 6 MONTHS	95
FIGURE 3.24: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS.....	97
FIGURE 3.25: EVIDENCE NETWORK FOR QUALITY OF LIFE AMONG TRIALS WITH A TREATMENT DURATION OF LESS THAN 6 MONTHS	98
FIGURE 3.26: EVIDENCE NETWORK FOR QUALITY OF LIFE AMONG STUDIES WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS.....	100
FIGURE 3.27: EVIDENCE NETWORK FOR ERECTILE FUNCTION AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS	101
FIGURE 3.28: EVIDENCE NETWORK FOR ERECTILE FUNCTION AMONG TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS	102
FIGURE 3.29: EVIDENCE NETWORK FOR LIBIDO AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS	104
FIGURE 3.30: EVIDENCE NETWORK FOR LIBIDO INVOLVING TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS.....	106
FIGURE 3.31: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS INVOLVING MEN AGED YOUNGER THAN 65 YEARS.....	107
FIGURE 3.32: EVIDENCE NETWORK FOR QUALITY OF LIFE INVOLVING MEN AGED LESS THAN 65 YEARS.....	110
FIGURE 3.33: EVIDENCE NETOWRK FOR OUALITY OF LIFE INVOLVING MEN AGED 65 YEARS AND OLDER	111
FIGURE 3.34: EVIDENCE NETWORK FOR ERECTILE DYSFUCNTION AMONG MEN AGED LESS THAN 65 YEARS	113

FIGURE 3.35: EVIDENCE NETWORK FOR LIBIDO AMONG MEN AGED LESS THAN 65 YEARS	115

CHAPTER 4

FIGURE 4.1: SELECTION OF STUDIES FOR INCLUSION IN THE SYSTEMATIC REVIEW (PRISMA)	149
FIGURE 4.2: RISK OF BIAS SUMMARY FOR INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST	152
FIGURE 4.3: ODDS RATIO OF CARDIOVASCULAR DEATH AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY	155
FIGURE 4.4: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH	156
FIGURE 4.5: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — CARDIOVASCULAR DEATH	159
FIGURE 4.6: ODDS RATIO OF MYOCARDIAL INFARCTION AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY	161
FIGURE 4.7: EVIDENCE NETWORK FOR MYOCARDIAL INFARCTION	162
FIGURE 4.8: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — MYOCARDIAL INFARCTION	164
FIGURE 4.9: ODDS RATIO OF STROKE AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY	166
FIGURE 4.10: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — STROKE	166
FIGURE 4.11: ODDS RATIO OF PROSTATE CANCER AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY	167
FIGURE 4.12: EVIDENCE NETWORK FOR PROSTATE CANCER	169
FIGURE 4.13: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — PROSTATE CANCER	171
FIGURE 4.14: ODDS RATIO OF A SERIOUS ADVERSE EVENT AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY, BY ROUTE	173
FIGURE 4.15: EVIDENCE NETWORK, SERIOUS ADVERSE EVENTS	172
FIGURE 4.16: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — SERIOUS ADVERSE EVENTS	176
FIGURE 4.17: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS	177
FIGURE 4.18: ODDS RATIO OF WITHDRAWAL DUE TO AN ADVERSE EVENT AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY, BY ROUTE	178
FIGURE 4.19: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — WITHDRAWALS DUE TO ADVERSE EVENTS	187
FIGURE 4.20: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH BY ROUTE OF ADMINISTRATION	192
FIGURE 4.21: EVIDENCE NETWORK FOR MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION	193
FIGURE 4.22: EVIDENCE NETWORK FOR PROSTATE CANCER, BY ROUTE OF ADMINISTRATION	195
FIGURE 4.23: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION	197

FIGURE 4.24: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION	199
FIGURE 4.25: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER	201
FIGURE 4.26: EVIDENCE NETWORK FOR PROSTATE CANCER AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER	204
FIGURE 4.27: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER	206
FIGURE 4.28: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS	208
FIGURE 4.29: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER	210
FIGURE 4.30: ODDS OF CARDIOVASCULAR DEATH AMONG PARTICIPANTS AGED LESS THAN 65 YEARS	214
FIGURE 4.31: ODDS OF MYOCARDIAL INFARCTION AMONG PARTICIPANTS AGED LESS THAN 65 YEARS	215
FIGURE 4.32: ODDS OF MYOCARDIAL INFARCTION AMONG PARTICIPANTS AGED MORE THAN 65 YEARS	215
FIGURE 4.33: ODDS OF STROKE AMONG PARTICIPANTS AGED MORE THAN 65 YEARS	216
FIGURE 4.34: ODDS OF PROSTATE CANCER AMONG PARTICIPANTS AGED LESS THAN 65 YEARS	217
FIGURE 4.35: ODDS OF PROSTATE CANCER AMONG PARTICIPANTS AGED MORE THAN 65 YEARS	218
FIGURE 4.36: ODDS OF A SERIOUS ADVERSE EVENT AMONG PARTICIPANTS AGED LESS THAN 65 YEARS	220
FIGURE 4.37: ODDS OF A SERIOUS ADVERSE EVENT AMONG PARTICIPANTS AGED MORE THAN 65 YEARS....	221
FIGURE 4.38: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS AMONG PARTICIPANTS AGED 65 YEARS AND OLDER	221
FIGURE 4.39: EVIDENCE NETWORK FOR WITHDRAWALS AMONG PARTICIPANTS AGED LESS THAN 65 YEARS	224
FIGURE 4.40: EVIDENCE NETWORK FOR WITHDRAWALS AMONG PARTICIPANTS AGED 65 YEARS AND OLDER	225

CHAPTER 5

FIGURE 5.1: RELATION BETWEEN STATISTICAL SIGNIFICANCE AND CLINICAL IMPORTANCE..	260

CHAPTER 1: INTRODUCTION

1.1 RATIONALE

The prescribing of testosterone products in Canada reached an all-time high in 2012 (1), yet the benefits and harms of these products are not clearly established. In general, efficacy trials have been small, used variable dosing regimens, and may have been unlikely to detect changes in outcomes important to patients or to provide an accurate estimate of adverse event rates (2). Despite claims by industry that testosterone products can restore vitality and improve quality of life, these claims have been only evaluated in small, short-term trials, and pooled analyses are lacking or out of date. Recently, an increased risk of cardiovascular-related events has been suggested by both observational and randomized studies.

In 2010, the Testosterone in Older Men with Mobility Limitations (TOM) trial, a randomized controlled trial involving 209 men aged 65 years and older with low testosterone and limited mobility was stopped early because of a higher rate of adverse cardiovascular events in the testosterone group than in the control group (3). As well, 2 retrospective observational studies have reported an association between the use of testosterone replacement therapy and cardiovascular events. In a retrospective database study, Finkle and colleagues (4) reported a higher rate of myocardial infarctions among men who filled a prescription for a testosterone product, with higher risk of an event among older men and among young men with a history of heart disease (4). Similarly, in a retrospective cohort study involving men who underwent angiography in the United States, Vigen and colleagues (5) reported an increased risk of a cardiovascular-related event among men with low testosterone who took a testosterone replacement product following angiography.

The results of previous meta-analyses of the risk of cardiovascular events associated with testosterone replacement therapy have been contradictory. In a 2014 meta-analysis, Corona and colleagues (6) reported no increased risk of a cardiovascular event among men taking testosterone. In contrast, an earlier systematic review published in 2013 reported an increased risk of cardiovascular-related events among men taking testosterone. However, direct comparison between these reviews is difficult because each used a different definition of “cardiovascular-related” event.

1.2 WHY IS A REVIEW NEEDED NOW?

Testosterone replacement products comprise a multi-billion dollar industry; however, the safety and efficacy of these products is not well established. Based on the early stoppage of the TOM trial (3) and the results of 2 observational studies (4, 5), Health Canada and the United States Food and Drug Administration have issued warnings about the potential for cardiovascular events among men with low testosterone due to aging. Previous systematic reviews and meta-analyses have included both hypogonadal (low testosterone level) and eugonadal (healthy testosterone level) men and have used composite outcomes to evaluate the risk of cardiovascular-related events. Despite the availability of dozens of testosterone products, most have never been compared in head-to-head trials, and there has been no network meta-analysis to evaluate their relative benefits and harms. In the current study, we summarized the current evidence for the benefits and harms of testosterone replacement therapies among men with androgen deficiency.

1.3 OBJECTIVES

The objective of this study was to determine the clinical benefits and harms of testosterone replacement therapy in adult hypogonadal men through a systematic review and Bayesian network meta-analysis.

1.4 RESEARCH QUESTIONS

1. What is the current evidence for the benefits and harms of testosterone replacement therapy in adult hypogonadal men?
2. Do the benefits or harms of testosterone replacement therapy vary based on route of administration, duration of treatment, patient age, or comorbidity?

1.5 OUTLINE

Each chapter describes a section of the thesis. Each chapter is briefly summarized below.

Chapter 1: This introductory chapter provides a summary of the rationale for the study, the objectives of the study, and an overview of the subsequent chapters.

Chapter 2: This chapter provides background on hypogonadism and testosterone replacement therapy, as well as a summary of previously published pooled studies of the benefits and harms associated with testosterone replacement products.

Chapter 3: This chapter presents the findings of a systematic review and network meta-analysis of the benefits of testosterone replacement therapy among hypogonadal men from randomized controlled trials.

Chapter 4: This chapter comprises a manuscript based on the results of systematic review and meta-analysis of harms of testosterone among hypogonadal men from randomized controlled trials. Harms data from included non-randomized studies of interventions are summarized narratively.

Chapter 5: This summary chapter places the results of the current study in the context of the existing literature. Limitations of the study are discussed, and an overall summary is provided.

1.6 REFERENCES

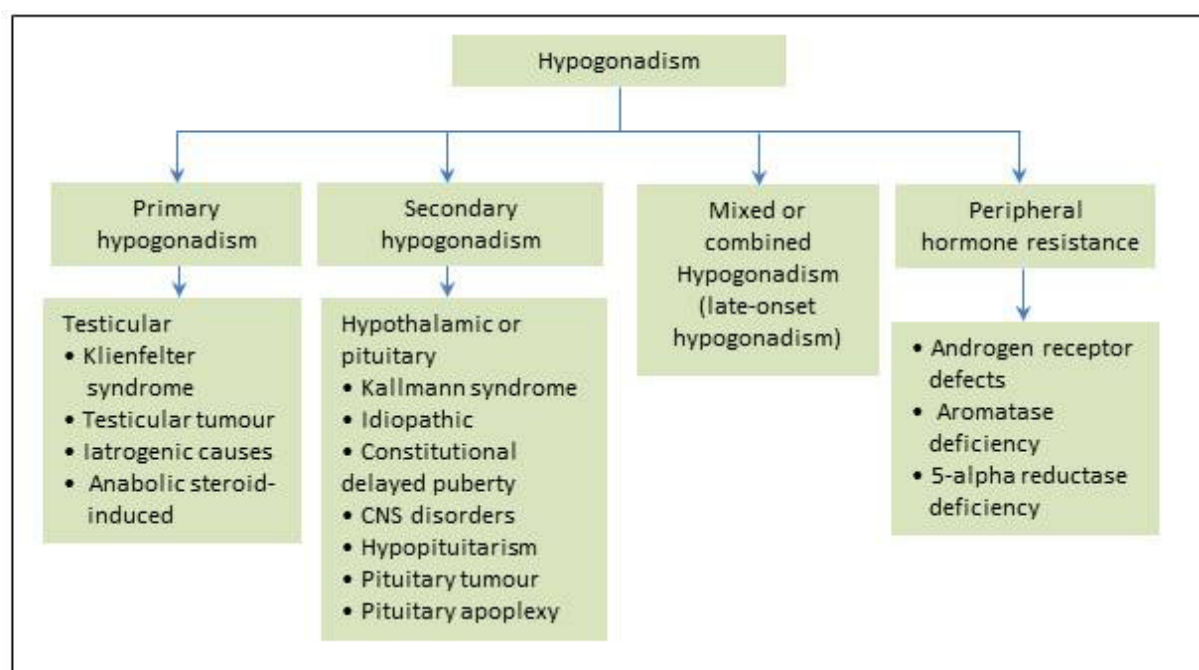
1. Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.
2. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-59.
3. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-22.
4. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PloS One* 2014;9(1):e85805.
5. Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829-36.
6. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug saf* 2014;13(10):1327-51.

CHAPTER 2: BACKGROUND

2.1 HYPOGONADISM

Hypogonadism, or androgen deficiency, is classified as primary or secondary hypogonadism when low androgen levels occur as result of testicular, hypothalamic, or pituitary dysfunction (Figure 2.1). Both primary and secondary hypogonadism can be congenital (e.g., Klinefelter syndrome, Y-chromosome microdeletions, mutations in luteinizing hormone or follicle-stimulating hormone receptors, Kallmann syndrome) or acquired (e.g., testicular trauma, radiation, chemotherapy, hyperprolactinemia, pituitary damage), and the signs and symptoms vary depending on the age of onset and the severity of the deficiency.

FIGURE 2.1: CAUSES OF REDUCED ANDROGEN LEVELS IN MEN. ADAPTED FROM ISIDORI 2014 (1).



The term “late-onset hypogonadism” is generally used to distinguish the age-related decline in testosterone in middle-aged (50–65 yr) and older (> 65 yr) men from the low testosterone levels associated primary or secondary hypogonadism. Late-onset hypogonadism is also referred to as “androgen deficiency in the aging male,” “andropause,” and “testicular

deficiency syndrome.” Starting in the mid-40s, testosterone levels in men decrease by about 1%–2% per year, with a more rapid decline among men in poor health (2).

Observational studies have suggested an association between reduced testosterone levels and reduced bone mineral density, muscle strength and mass, and physical function, and an increased risk of diabetes mellitus, metabolic syndrome, and anemia (3-8); however, these studies do not usually make a distinction between low testosterone due to aging or primary/secondary hypogonadism. Hypogonadal men may also experience decreased libido (9), erectile function (10), and quality of life (11), as well as increased depression (12). Cross-sectional studies have reported that testosterone levels are lower among men with cardiovascular disease than among the general population and that low testosterone is correlated with increased risk of cardiovascular mortality (13); this effect may be more pronounced among men with diabetes or hypertension (13). The presence of confounding factors, such as age, makes interpretation of these findings difficult.

2.2 DIAGNOSIS OF HYPOGONADISM

The diagnosis of hypogonadism is generally made based on low serum testosterone levels and clinical signs and symptoms. The most recent clinical practice guidelines by The Endocrine Society (14) recommend that the diagnosis be made based on repeated “unequivocally low” serum testosterone levels and symptoms consistent with androgen deficiency (Table 2.1); however, the guidelines do not specify the number of signs or symptoms required for diagnosis. The authors note, however, that the signs and symptoms are non-specific and that they may vary by age, comorbid illness, severity and duration of testosterone deficiency, and by the previous use of testosterone therapy (14).

There is no universally accepted definition of what constitutes a “low” testosterone level. The International Society of Andrology (ISA), International Society for Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Association of Andrology (EAA), and the American Society of Andrology (ASA) recommend that patients with testosterone concentrations below 8 nmol/L be considered for testosterone replacement therapy and that patients with a concentration above 12.1 nmol/L require no treatment (15). For patients with a total testosterone concentration between 8 and 12 nmol/L, the

ISA/ISSAM/EAU/EAA/ASA recommend that free testosterone concentration should be calculated or measured directly (15) (Table 2.2).

There are no explicit Canadian guidelines for the diagnosis of androgen deficiency. General guidelines published in 2010 by a Canadian group of researchers with ties to pharmaceutical companies that manufacture testosterone replacement products do not define a “normal” range (16). Morales and colleagues (16) recommend that the diagnosis be based on bioavailable testosterone levels, and they do not state whether signs and symptoms should be considered in the diagnosis.

TABLE 2.1: SIGNS AND SYMPTOMS SUGGESTIVE OF ANDROGEN DEFICIENCY IN MEN

More specific symptoms and signs	Other less specific symptoms and signs
• Incomplete or delayed sexual development, eunuchoidism	• Decreased energy, motivation, initiative, and self-confidence
• Reduced sexual desire (libido) and activity	• Feeling sad or blue, depressed mood, dysthymia
• Decreased spontaneous erections	• Poor concentration and memory
• Breast discomfort, gynecomastia	• Sleep disturbance, increased sleepiness
• Loss of body (axillary and pubic) hair, reduced shaving	• Mild anemia
• Very small (especially < 5 ml) or shrinking testes	• Reduced muscle bulk and strength
• Inability to father children, low or zero sperm count	• Increased body fat, body mass index
• Height loss, low trauma fracture, low bone mineral density	• Diminished physical or work performance
• Hot flushes, sweats	

Note: Adapted from Bhasin et al., 2010 (14).

2.3 EPIDEMIOLOGY

The Baltimore Longitudinal Study of Aging, a population-based study of aging in the United States involving 890 men, found that the prevalence of low testosterone (serum total testosterone: < 11.3 nmol/L) increased with increasing age (50–59 yr: 12%; 60–69 yr: 19%; 70–79 yr: 28%; > 80 yr: 49%). The participants in this study were primarily white (87%) middle-class men with few comorbidities (18). The prevalence of hypogonadism in the

TABLE 2.2: GUIDELINES FOR THE DIAGNOSIS OF HYPOGONADISM IN MEN

Guideline	Endocrine Society (14)	ISA/ISSAM/EUA/EAA/ASA (15)	British Society for Sexual Medicine (17)	Morales et al.,* (16)
Normal T level	Use lower limit of normal established in laboratory (lower limit in some laboratories is 9.8–10.4 nmol/L (total T))	Total T > 12 nmol/L does not require TRT; levels between 8 and 12 usually benefit from testosterone replacement	Total T > 12 nmol/L does not require TRT; levels below 8 nmol/L usually benefit from testosterone replacement	Not defined
Fraction to be measured	Total T (free or bioavailable T if the total level is near the lower limit of normal)	Total T (free T if the total level is near the lower limit of normal)	Total T	Bioavailable T
Diagnosis based on consistent signs/symptoms and low T levels	Yes	Yes	Yes	Not stated

Note: ISA/ISSAM/EUA/EAA/ASA = The International Society of Andrology (ISA), International Society for Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Association of Andrology (EAA), and the American Society of Andrology (ASA), T = testosterone, TRT = testosterone replacement therapy.
 *Not an official guideline. This document was authored by a group of Canadian researchers and was sponsored by Abbott (makers of Androgel 1% testosterone gel).

general population was reportedly higher in the Massachusetts Male Aging Study (25% among men aged 45–70 yr); however, they used a less stringent cut-off for “low” testosterone (< 13.9 nmol/L) (19). The authors extrapolated these data to estimate 481,000 new cases of androgen deficiency per year among men aged 40–69 years in the United States (19).

The prevalence of low testosterone among men in primary care may be higher. In the Hypogonadism in Males study, a survey of 2165 male primary care patients in the United States aged 45 years or older (mean 60.5 yr), the prevalence of low testosterone (< 10.4 nmol/L) was 36.3% (95% confidence interval [CI] 34.2% to 38.4%) among men not receiving androgen therapy, and the prevalence increased with increasing age (20).

Of male respondents to the Boston Area Community Health Survey aged 30–79 years (mean 47.3 yr; n = 1475), 24% had a total testosterone level below 10.4 nmol/L; of these, 5.6% (95% CI 3.6% to 8.6%) reported symptoms of androgen deficiency (1 of low libido, erectile dysfunction, osteoporosis, or fracture, or 2 of sleep disturbance, depressed mood, lethargy, or diminished physical performance). The prevalence of symptomatic androgen deficiency

was not related to ethnic background; however, prevalence was higher among men aged greater than 70 years (18.4%) compared with men aged less than 70 years (3.1%–7%) (21).

There are limited data about the prevalence of hypogonadism in Canada. A 2000 study involving 316 Canadian physicians estimated that 25% had a bioavailable testosterone level below 70 nmol/L, and the proportion of men with low testosterone increased with advancing age (22).

Whether the incidence of hypogonadism over time is changing is not unknown. The past 2 decades have seen a dramatic increase in the number of men prescribed testosterone replacement therapy (23); however, whether this is because of increased marketing of testosterone replacement products, societal pressure to stay young, or a true increase in incidence is not known.

2.4 TESTOSTERONE REPLACEMENT THERAPY

There are 12 testosterone replacement products approved for use in Canada in adult men “who are experiencing medical conditions because their body cannot make enough testosterone” (24). Health Canada states that these products should not be used in men with non-specific symptoms if low testosterone has not been confirmed via laboratory testing (24). There are roughly another 2 dozen testosterone products available worldwide.

Testosterone products can be broadly grouped by route of administration (oral, topical, intramuscular injection), and there are multiple formulations available (e.g., testosterone, testosterone undecanoate, testosterone cypionate, testosterone enanthate) (Table 2.3).

The US Food and Drug Administration has also approved testosterone replacement products for use only in men with low testosterone in combination with an underlying medical condition (e.g., primary or secondary hypogonadism, or as a result of chemotherapy) (25). They do not approve the use of testosterone replacement products in men with low testosterone as a result of the natural aging process.

Each testosterone product is associated with its own advantages and disadvantages (Table 2.3). For example, testosterone gels are convenient and easy to apply, but they must be

applied daily and there is a risk of transfer to others (e.g., children). Other products, such as testosterone esters administered by intramuscular injection are administered more infrequently (up to 12 wk between dose depending on product) but there may be pain associated with the injection, and testosterone levels may vary widely between injections.

TABLE 2.3: CHARACTERISTICS OF TESTOSTERONE REPLACEMENT PRODUCTS (26)

Product	Route of administration	½ life	Approved in Canada?	Advantages	Disadvantages
Testosterone gel	Topical	6 h	1% gel, liquid	-convenient -easy to apply	-daily application -possible transfer to others -odor -messy
Testosterone patch	Topical (scrotal or non-scrotal)	10 h	Non-scrotal patches only	-may mimic circadian rhythm -convenient -minimal transmission	-skin irritation -daily application
Testosterone esters	Intramuscular injection	4-34 d depending on ester	Yes: testosterone enanthate, testosterone cypionate No: testosterone undecanoate	-administered infrequently (depending on formulation) - inexpensive	-wide swings in testosterone levels over time -requires injection -pain
Testosterone pellets	Subcutaneous	3 mo	No	-convenient - no risk of transmission - high compliance	-requires small incision -high rate of extrusion
Buccal testosterone	Buccal		No	-convenient	-mouth irritation
Oral testosterone	Oral	4 h	Yes	-convenient	-variable clinical response

2.5 CLINICAL PRACTICE GUIDELINES

Based on the results of 3 systematic reviews (27-29), the Endocrine Society published guidelines in 2010 that recommend testosterone replacement therapy for “symptomatic men with classical androgen deficiency syndromes,” with the goal of inducing and maintaining secondary sex characteristics and improving sexual function, sense of well-being, and bone mineral density (14). The Endocrine Society’s guidelines caution that patients should be monitored and evaluated for adverse events such as fluctuations in mood or libido, cough (following injection), erythrocytosis, and skin reactions. For older men, testosterone

replacement therapy may be offered after low testosterone is observed more than once and if the patient has “clinically significant symptoms” of androgen deficiency; however, the number and type of “clinically significant symptoms” are not described. The level of testosterone considered “low” is not explicitly described in the guidelines, but the authors note that the threshold for most symptoms corresponds to the lower limit of the normal range for young men (10.4 nmol/L) (14).

The clinical practice guidelines by the Endocrine Society recommend against testosterone replacement therapy for men with prostate cancer (or high prostate specific antigen levels), elevated hematocrit levels (> 50%), obstructive sleep apnea, lower urinary tract symptoms caused by an enlarged prostate, poorly controlled heart failure, or breast cancer (14).

No new guidelines have been published since 2010, despite the publication of several randomized controlled trials, systematic reviews, and meta-analyses.

2.6 WHAT IS CURRENTLY KNOWN

2.6.1 BENEFITS

The benefits of testosterone replacement products are purported to be wide ranging. Advertising campaigns, such as the “Has He Lost That Loving Feeling?” campaign by Abbott Canada in 2011 (30), and the “Low T Centre” (www.lowtcenter.com) in the United States suggest that testosterone replacement therapy can improve quality of life and restore vitality and youth. However, these claims not been evaluated (e.g., restoration of “youth”) or have been investigated in small trials for short durations (e.g., libido, quality of life, erectile dysfunction), and pooled analyses are largely lacking or out of date.

A 2007 systematic review and meta-analysis involving men with sexual dysfunction and low testosterone found no significant effect of testosterone replacement therapy on erectile function (4 trials, standardized mean difference [SMD] 0.80, 95% CI –0.10 to 1.60), but a significant effect on libido (5 trials; SMD 1.31, 95% CI 0.40 to 2.22) (27); however, 2 of the included trials were short duration crossover trials (31, 32), and the mean testosterone level of 1 trial was above the generally accepted limit for low testosterone (12 nmol/L) (33).

The effect of testosterone replacement therapy on quality of life has not been evaluated in a pooled analysis. Some primary studies have suggested that testosterone supplementation may improve quality of life (34, 35), although others have reported no significant effect (36, 37).

A 2009 meta-analysis reported a significant effect of testosterone on depression (38); however, only studies that enrolled patients with depression at baseline and that evaluated depression using the Hamilton Rating Scale for Depression were considered eligible for this analysis.

2.6.2 HARMS

Despite over 70 years of use, risks of testosterone replacement therapy are still unclear. In general, most studies involving testosterone replacement therapy have been small efficacy trials with a limited duration that were unlikely to provide an accurate estimate of adverse event rates.

There has been increasing concern in recent years about the risk of adverse events among men taking testosterone replacement products. The Testosterone in Older Men with Mobility Limitations (TOM) trial, a randomized controlled trial (RCT) involving 209 community-dwelling men aged 65 years and older with low testosterone (< 12.1 nmol/L) and limited mobility was stopped early because of a higher rate of adverse cardiovascular events in the testosterone group than in the control group (39); there was also a higher rate of respiratory, thoracic, and mediastinal disorders, and skin and subcutaneous tissue disorders in the testosterone group than in the control group. The increased risk of cardiovascular events in the testosterone group was also observed during a 3-month observation period following discontinuation of the intervention (39). The difference in risk between groups was still significant after adjustment for age, body mass index, smoking, high-density lipoprotein cholesterol level, diabetes, hyperlipidemia, and hypertension. The authors note that the dose of testosterone used was higher than typically considered in clinical practice (although the dose used was consistent with that used in other testosterone trials and is at the upper end of the recommended dose), and that there was a high prevalence of comorbidities among the included men (pre-existing heart disease, obesity, diabetes, hypertension).

A recent observational study in the United States evaluated the association between the use of testosterone replacement therapy and cardiovascular events among men who filled a prescription for a testosterone product (n = 55,593; mean 54.4 yr) compared with men who filled a prescription for a phosphodiesterase type 5 inhibitor (PDE5I; n = 167,279; mean 56.0 yr) (40). The testosterone level of patients in either cohort was not available. Among men prescribed a testosterone replacement product, the rate ratio of myocardial infarction (after v. before) was 1.36 (95% CI 1.03 to 1.81). Compared to men who had filled a prescription for PDE5I, men who filled a testosterone prescription were more likely to have a myocardial infarction during the follow-up period (adjusted ratio of rate ratios [RRRs] 1.27, 95% 0.94 to 1.71) (Ratio of rate ratios: ratio of the rate of events after treatment to the rate before treatment in the testosterone group over that in the comparison group.) The risk was higher among men older than 65 years (RR 2.19 [95% CI 1.27 to 3.77]; adjusted RRR: 1.90 [95% CI 1.04 to 3.49]) and among younger men (< 65 yr) with a history of heart disease (RR 2.90, 1.49 to 5.62; adjusted RRR 2.07, 95% CI 1.05 to 4.11) (40).

A second observational study has also raised concerns about the harms of testosterone replacement products. Vigen and colleagues (41) performed a retrospective cohort study of men with low testosterone (< 10.4 nmol/L) who had undergone coronary angiography (n = 8709). A total of 1710 cardiovascular events (composite: all-cause mortality, myocardial infarction, ischemic stroke) occurred during follow-up among those taking a testosterone product (n = 1223), compared to 681 events among 7486 patients not taking testosterone (absolute risk difference 5.8%, 95% CI -1.4% to 13.1%).

Meta-analyses of the potential harms associated with the use of testosterone replacement therapies have been performed; however, the results have been contradictory, and direct comparison between reviews is difficult because of different included populations, durations of treatment, and outcome definitions (Table 2.4).

The systematic review by Corona and colleagues (44) involving 75 placebo-controlled RCTs (5464 men) of any duration found no increased risk of cardiovascular events among men using testosterone replacement therapies (45). Their English-language search covered the period from 1969 to January 31, 2014, and they included studies with both eugonadal and hypogonadal men. The author's primary outcome was a composite outcome that they termed

TABLE 2.4: CHARACTERISTICS OF SYSTEMATIC REVIEWS EVALUATING HARMS ASSOCIATED WITH TESTOSTERONE REPLACEMENT THERAPY

Characteristic	Calof 2005 (42)	Haddad 2007 (28)	Fernandez-Balsells 2010 (29)	Xu 2013 (43)	Corona 2014 (44)
Study designs	RCT	RCT	RCT, NRS*	RCT	RCT
No. of trials	19	6	51	27	75
Duration	3 mo	No restriction	3 mo	3 mo	No restriction
Hypogonadal or eugonadal	Mixed	Mixed	Mixed	Mixed	Mixed
Hypogonadal subgroup analysis	No	No	No	No	CV events: OR 0.84 (0.32 to 2.23)
CV death	—	—	—	—	OR 1.14 (0.49 to 2.66)
Myocardial infarction	OR 0.99 (0.44 to 2.26)	OR 2.24 (0.50 to 1.02)	RR 0.91 (0.29 to 2.82)	—	OR 0.68 (0.3 to 1.52)
Stroke	—	—	—	—	OR 0.82 (0.24 to 2.83)
Serious adverse events	—	—	—	—	—
Any CV/composite event	CV-events (not defined): OR 1.14 (0.59 to 2.20)	Composite: CV-related event: OR 1.82 (0.78 to 4.23)	—	Composite: CV-related event (cardiac disorder, cardiovascular complaints, CV events, vascular disorders) OR 1.54 (1.09 to 2.18)	Composite: CV-related event (non-fatal MI, CV death, stroke, ACS, HF) OR 1.01 (0.57 to 1.77)
Prostate cancer	OR 1.09 (0.48 to 2.49)	—	RR 0.79 (0.28 to 2.28)	—	—
Other	All-cause death: OR 0.78 (0.32 to 1.93)	—	All-cause mortality: RR 1.12 (0.70 to 1.81) Diabetes: RR 0.67 (0.12 to 3.67)	—	ACS: 0.92 (0.43 to 1.97) HF: 1.64 (0.25 to 10.63)

Note: ACS = acute coronary syndrome, CV = cardiovascular, HF = heart failure, MI = myocardial infarction, NRS = non-randomized studies, OR = odds ratio, RCT = randomized controlled trials, RR = relative risk.
 *Results from NRS appear to have been included with results from RCTs in their meta-analysis.

major adverse cardiovascular event (MACE), and included cardiovascular death, non-fatal acute MI, stroke, acute coronary syndromes, and heart failure reported as a serious adverse events; however this is a non-standard definition of MACE, and the authors summed individual events reported in the primary trials to make their MACE outcome (e.g., if 1

stroke and 2 myocardial infarctions occurred, they deemed this to represent 3 MACE events). Of the 75 included trials, 26 trials contributed data to their primary outcome analysis. They found no increased risk of MACE associated with the use of testosterone products (OR 1.01, 95% CI 0.57 to 1.77), and no increased risk with the individual components of the composite outcome.

A systematic review published in 2013 that included placebo-controlled randomized trials (27 trials, 2994 men) of testosterone therapy (> 12 wk duration) reported an increased risk of a cardiovascular-related events (OR 1.54, 95% CI 1.09 to 2.18) with testosterone therapy compared to placebo (43). The authors of this trial also used a composite outcome, comprised of cardiac disorders, cardiovascular complaints, cardiovascular events, and vascular disorders. The trials included in this study ranged from 12 weeks to 3 years, and the authors did not perform subgroup analysis based on hypogonadal status (43).

An earlier systematic review including 51 studies published up to August 2008 with a minimum treatment duration of 3 months found no significant difference in all-cause mortality, prostate cancer, or myocardial infarction (29); studies enrolling both hypogonadal and eugonadal participants were included in this analysis. Earlier studies also reported no differences in cardiovascular-related events (28, 42) (Table 2.4).

2.7 WHY IS A REVIEW NEEDED NOW?

From 2000 to 2011, global sales of testosterone products increased 12-fold (46) and were estimated to top US\$2 billion in 2012 (47). A recent analysis of prescribing patterns in Canada among men aged 66 years and older reported that prescribing rose by 286% from 1997 to 2003, with a plateau in 2004 and 2005 due to changes in reimbursement strategies (23). By 2012, testosterone prescriptions had reached an all-time high in Canada (11 per 1000 eligible men) (23). Of note, only 6.3% of men prescribed a testosterone product had a documented diagnosis of hypogonadism (23), suggesting a high proportion of inappropriate prescribing and/or use. There have been no new indications added for testosterone prescription during this period, and it is unlikely that the sharp increase in testosterone prescribing over the past decade was due to an increase in diagnosed androgen deficiency syndrome. Advertising campaigns, such as the “Has He Lost That Loving Feeling?”, and an

aging population are likely partly responsible for the increased use of testosterone products. However, concerns about the safety of these products exist, including increased risk of cardiovascular events and death. Health Canada and the US Food and Drug Administration have both cautioned against the inappropriate prescribing of these agents (25, 48).

Most testosterone trials have been placebo-controlled, although there have been a few head-to-head trials. To date, there has been no network meta-analysis directly comparing the benefits or harms of testosterone replacement therapies. Because of the unique properties of each product, we believe that network meta-analysis is an ideal method to compare the benefits and harms of these products with each other, as well as with placebo. In this study, we sought to perform a head-to-head analysis of the benefits and harms of testosterone replacement therapy using a network meta-analysis approach.

2.8 REFERENCES

1. Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. *Eur Urol* 2014;65(1):99-112.
2. Feldman HA, Longcope C, Derby CA, et al.. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab* 2002;87(2):589-98.
3. van den Beld AW, de Jong Fh, Grobbee DE, Pols Ha, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 2000;85(9):3276-82.
4. Roy TA, Blackman MR, Harman SM, Tobin JD, Schrager M, Metter EJ. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. *Am J Physiol Endocrinol Metab* 2002;283(2):E284-94.
5. Orwoll E, Lambert LC, Marshall LM, Blank J, Barrett-Connor E, Cauley J, Ensrud K, et al. Endogenous testosterone levels, physical performance, and fall risk in older men. *Arch Intern Med* 2006;166(19):2124-31.
6. Jackson JA, Riggs MW, Spiekerman AM. Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. *Am J Med Sci* 1992;304(1):4-8..
7. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen T-P, Valkonen V-P, Salonen R, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004;27(5):1036-41.
8. Ferrucci L, Maggio M, Bandinelli S, Basaria S, Lauretani F, Ble A, Valenti G, et al. Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med* 2006;166(3):1380-8.

9. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. *J Clin Endocrinol Metab* 2006;91(7):2509-13.
10. Kohler TS, Kim J, Feia K, Bodie J, Johnson N, Makhoulouf A, Monga M, et al. Prevalence of androgen deficiency in men with erectile dysfunction. *Urology* 2008;71(4):693-7.
11. Novak A, Brod M, Elbers J. Andropause and quality of life: findings from patient focus groups and clinical experts. *Maturitas* 2002;43(4):231-7.
12. Joshi D, van Schoor NM, de Ronde W, Schaap LA, Comijs HC, Beekman ATF, Lips P, et al. Low free testosterone levels are associated with prevalence and incidence of depressive symptoms in older men. *Clin Endocrinol (Oxf)* 2010;72(2):232-40.
13. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol* 2011;165(5):687-701.
14. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(6):2536-59.
15. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Int J Impot Res* 2009;21(1):1-8.
16. Morales A, Bella Aj, Chun S, Lee J, Assimakopoulos P, Bebb R, Gottesman I, et al. A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians. *Can Urol Assoc J* 2010;4(4):269-75.
17. Wylie K, Rees M, Hackett G, Anderson R, Bouloux P-M, Cust M, Goldmeier D, et al. Androgens, health and sexuality in women and men. *Maturitas* 2010;67(3):275-89.
18. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2010;86(2):724-31.
19. Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: Estimates from the Massachusetts male aging study. *J Clin Endocrinol Metab* 2004;89(12):5920-6.
20. Mulligan T, Frick MF, Zuraw QC, Stenham A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006;60(7):762-9.
21. Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007;92(11):4241-7.
22. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, Perry HM, 3rd, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000;49(9):1239-42.
23. Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.
24. Canada H. Summary Safety Review - Testosterone Replacement Products - Cardiovascular Risk 2014 [cited April 15, 2015]. Available: www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/testosterone-eng.php.
25. Administration UFaD. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of

- possible increased risk of heart attack and stroke with use. 2015 [cited May 11, 2015]. Available: www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf.
26. McGill JJ, Shoskes DA, Sabanegh ES. Androgen deficiency in older men: indications, advantages, and pitfalls of testosterone replacement therapy. *Cleve Clin J Med* 2012;79(11):797-806.
 27. Bolona ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82(1):20-8.
 28. Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82(1):29-39.
 29. Fernandez-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, et al. Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010; 95(6):2560-2575.
 30. Eggertson L. Brouhaha erupts over testosterone-testing advertising campaign. *CMAJ* 2011;183(16):E1161-2.
 31. Carani C, Zini D, Baldini A, Della CL, Ghizzani A, Marrama P. Effects of androgen treatment in impotent men with normal and low levels of free testosterone. *Arch Sex Behav* 1990;19(3):223-34.
 32. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clinical Endocrinology* 1981;14(1):49-61.
 33. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84(6):1966-72.
 34. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med* 2013;10(6):1612-27.
 35. Zhang XW, Liu ZH, Hu XW, Yuan YQ, Bai WJ, Wang XF, et al. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. *Chin Med J* 2012;125(21):3806-10.
 36. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res* 2009;21(2):129-38.
 37. Spitzer M, Basaria S, Travison TG, Davda MN, Paley A, Cohen B, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med* 2012;157(10):681-91.
 38. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract* 2009;15(4):289-305.
 39. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-22.
 40. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PloS One* 2014;9(1):e85805, 2014.

41. Vigen R, O'Donnell C, Baron AE, Grunwald G, Maddox TM, Bradley SM, Barqawi A, et al. Association of testosterone replacement therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829-1836.
42. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 2005;60(11):1451-7.
43. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Medicine*. 2013;11:108.
44. Corona G, Maggi M. Testosterone supplementation and cardiovascular risk. *Trends Cardiovasc Med* 2015;25(3):258-60.
45. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014;13(10):1327-51.
46. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. *Med J Aust* 2013;199(8):548-51.
47. Rosenthal E. A push to sell testosterone gels troubles doctors: The New York Times; 2013 [cited April 15, 2015]. Available: www.nytimes.com/2013/10/16/us/a-push-to-sell-testosterone-gels-troubles-doctors.html?_r=0.
48. Canada H. Information update: Possible cardiovascular problems associated with testosterone products 2014 [cited April 15, 2015]. Available: <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/40587a-eng.php>.

CHAPTER 3: BENEFITS OF TESTOSTERONE REPLACEMENT THERAPY AMONG HYPOGONADAL MEN

3.1 INTRODUCTION

Testosterone replacement therapy is generally touted as way to restore youthful energy, improve sexual health, and elevate mood and quality of life. These products are widely marketed to the general population, and their sales increased by about 65% between 2009 and 2013 in the United States (1); men aged 40–60 years make up the largest group using these products (2). However, the efficacy of testosterone in meeting these claims is unclear. In their 2010 clinical practice guidelines, the Endocrine Society recommended testosterone replacement therapy for men with sexual dysfunction and low testosterone levels as a way to improve libido and erectile function; however, this was a weak recommendation based on low to very low levels of evidence. In both Canada and the US, testosterone replacement products are approved for use in men with low testosterone as a result of a medical condition (e.g., testicular [primary hypogonadism] or hypothalamic or pituitary [secondary hypogonadism] conditions), and the US Food and Drug Administration cautions that both the benefits and harms of testosterone replacement therapy for age-related hypogonadism have not been established (3).

Previous systematic reviews have primarily focused on the safety of testosterone replacement therapy (4-6), and pooled analyses of the benefits of testosterone replacement therapy are lacking or out-of-date. Although quality of life among men taking testosterone products has been assessed in multiple randomized controlled trials (RCTs), there has been no summary analysis of its effects. A 2009 meta-analysis reported that testosterone supplementation may improve symptoms of depression among hypogonadal men with depression at baseline (7), and a 2014 meta-analysis reported that testosterone was effective at improving depressive symptoms among hypogonadal men with or without depression (8). A 2007 systematic review and meta-analysis involving men with sexual dysfunction and low testosterone found no significant effect of testosterone replacement therapy on erectile function, but a significant effect on libido (9).

There are dozens of testosterone products currently available worldwide, although their individual availability depends on jurisdiction. Testosterone products are manufactured in a variety of formulations (e.g., testosterone undecanoate, testosterone enanthate, testosterone cypionate) and routes of administration (e.g., topical, oral, intramuscular injection). Each formulation is associated with advantages and disadvantages with respect to convenience, transmission to others, and ease of administration; however, it is unknown whether the benefits of each product are similar, and most have not been compared in head-to-head trials. Network meta-analysis allows the integration of direct evidence from primary studies with indirect evidence (comparison of 2 treatments that share a common comparator). This technique allows inferences to be made as to the relative benefits of treatments that have not been directly compared in head-to-head trials. Our objective was to summarize the current evidence from RCTs for the benefits of testosterone replacement therapy for improving depression, quality of life, erectile function, libido, and testosterone levels among adult men with hypogonadism.

3.2 METHODS

This systematic review followed the network meta-analysis extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-NMA) checklist (10) and the Cochrane Handbook for Systematic Reviews of Interventions (11). The protocol was registered before study selection was initiated (PROSPERO no.: CRD42014009963).

3.2.1 SEARCH STRATEGY

Relevant RCTs were identified through a comprehensive search of the Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase Classic+Embase, and Cochrane Central Register of Controlled Trials (June 8, 2014). The search strategies (Appendix 1) were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Strategies used a combination of controlled vocabulary (e.g., testosterone, androgens, androgen therapy) and keywords (e.g., Delatestryl, testosterone supplementation, testosterone replacement therapy), and the vocabulary and syntax were adjusted across the databases. We used research design filters to identify randomized, non-randomized, and controlled clinical trials, as well as

observational (comparative) studies. A grey literature search of relevant databases and web sites was performed using resources listed in CADTH's *Grey Matters Light*.

3.2.2 STUDY SELECTION

We included RCTs involving adult men (≥ 18 yr) with low testosterone (serum total testosterone ≤ 12 nmol/L or free testosterone < 225 pmol/L) (12). All testosterone products were eligible for inclusions, but testosterone precursors (e.g., dehydroepiandrosterone [DHEA]) were excluded. Studies that artificially suppressed endogenous testosterone levels or involved a non-pharmacologic intervention were excluded. The comparator could be placebo, a different testosterone product, or the same testosterone product at a different dose. We excluded trials with less than 10 participants (to avoid capturing case series and anecdotal evidence) or less than 12 weeks' duration of treatment. A 12-week minimum duration was chosen to allow stabilization of testosterone levels before outcome assessment and has been used in previous meta-analyses (4,6). Decisions about duration and trial size were made in consultation with clinical experts. Cross-over trials were included if the initial period was at least 12 weeks' duration; data from cross-over trials were included in the data analysis if the first-period data were reported separately for each treatment group. Abstracts were not excluded; however, data from abstracts were not included in data analyses. Comparative observational (non-randomized) studies of interventions were eligible for inclusion in the systematic review; however, only data from RCTs are summarized for benefits outcomes. Studies were not excluded based on outcome.

Two independent review authors (J.E., J.P.) applied the eligibility criteria to each title and abstract identified in the literature search. Any trial that was considered to be relevant by 1 reviewer was reviewed in full-text format by 2 independent reviewers (J.E., J.P., A.J.), and a final decision made for inclusion. Any uncertainties were resolved by discussion and consensus with a third review author (S.K.). Reviewers were not blinded as to study authors or centre of publication prior to study selection.

3.2.3 OUTCOMES

The primary outcomes were depression, quality of life, erectile function, and libido at the end of the treatment period, measured by use of a scale. If the end of study was not equivalent to the end of treatment (e.g., no-treatment follow-up period), data were extracted and analyzed for the end of the treatment period. Serum total testosterone levels were analyzed at 3 months, 6 months, and at the end of the treatment period.

3.2.4 DATA EXTRACTION

One reviewer extracted data from the included RCTs, and a second reviewer checked the data for accuracy (J.E., J.P., A.J., A.K.). We extracted characteristics of trial participants, trial characteristics (including funding source), details on each trial arm, including but not limited to dose, frequency, route of administration, and duration of treatment. Data for clinical efficacy were extracted as presented by the authors and converted to a standard unit before analysis where appropriate (e.g., testosterone levels). Extraction was conducted using standardized data abstraction forms in DistillerSR, and all extraction forms were piloted before extraction. The original, primary publication for each unique trial was included and used for data extraction, except if multiple publications for a single trial were found. Multiple publications (e.g. supplemental online appendices, companion publications of specific outcomes or populations from the original trial) were handled by extracting the most recent and detailed data for each outcome. Data for safety outcomes were also extracted and are summarized in Chapter 4.

3.2.5 RISK OF BIAS

Risk of bias was assessed by use of the Cochrane Collaboration's tool for assessing risk of bias for RCTs. We assessed blinding (participants, personnel, outcome assessors) separately for objective and subjective outcomes. Total testosterone level was considered to be an objective outcome, while depression, quality of life, libido, and erectile function were considered to be subjective outcomes. We considered incomplete outcome data separately for benefits and harms outcomes; harms outcomes are summarized in Chapter 4. We did not assess other potential threats to validity or selective outcome reporting.

3.2.6 PUBLICATION BIAS

Funnel plots were used to assess potential publication bias for each outcome. The standard error (SE) for each estimate was plotted (vertical axis) against the standardized mean difference (SMD; horizontal axis). The pooled estimate is plotted as a vertical dashed line. Trials with a smaller SE for the estimate (more precision; generally larger trials) will fall higher on the graph, while estimates with larger SE (less precise estimates) will be lower on the graph. Less precise estimates would be expected to be more affected by chance, and we would expect to see a wider scatter of points at the bottom of the plots, giving an inverted funnel shape, in the absence of publication bias.

3.2.7 STATISTICAL ANALYSIS

We performed Bayesian mixed-treatment comparison meta-analyses for the following outcomes: depression, quality of life, erectile function, libido, and total testosterone level. The effect size for total testosterone level was expressed in terms of the mean difference (MD; between group difference unadjusted for baseline). For continuous outcomes reported using different scales (i.e., depression, quality of life, erectile function, libido), SMDs were calculated. Scales were converted to a common direction before analysis. The number of participants randomized (intention-to-treat population) was used in all analyses. Each node in the network represents a testosterone product at a specified dose.

One trial (13) based its testosterone dosing strategy on each participant's baseline level of total testosterone (patients with total testosterone < 8 nmol/L received 160 mg/d, patients with testosterone between 8 and 12 nmol/L received 120 mg/d). This dosing strategy was included as a separate node in the network (referred to as "T-based dose [120 or 160 mg/d]") because the data were not provided separately by dose.

Cavallini and colleagues (14) reported outcome data as median (range); for the purpose of our analysis, we assumed mean to be equal to median and that SD was equal to one-quarter of the range.

Trials that involved treatment with Nebido (intramuscular testosterone undecanoate, 1000 mg) were grouped together based on the typical dosing schedule (baseline, wk 6, wk 12, followed by injections every 12 weeks).

We used WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) to conduct Bayesian network meta-analyses using a binomial likelihood model, which allows for the use of multi-arm trials (15, 16). Placebo was chosen as the reference group (index node) in the model. Both fixed- and random-effects network meta-analyses were conducted; assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points (15, 17). For both DIC and residual deviance, a lower value indicates better model fit. For outcomes in which the deviance information criterion and residual deviance were similar between models, the random-effects model was chosen to account for heterogeneity in the trial population. Point estimates, 95% credible intervals, and SDs were derived using Markov Chain Monte Carlo methods. Three chains were fit in WinBUGS for each analysis, with at least 10 000 iterations, and a burn-in of at least 10 000 iterations. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout (15). Convergence of the model was assessed by examining Brooks-Gelman-Rubin plots; convergence is suggested when the Gelman-Rubin statistic approaches 1.0 (18). Consistency was evaluated where possible by plotting the deviance from the consistency and inconsistency models. All network diagrams were constructed using NodeXL.

Pair-wise meta-analysis (versus placebo) was performed for outcomes with insufficient data for network meta-analysis. Model choice (fixed or random effects) was based on statistical and clinical heterogeneity.

Key for colour-coded results tables: Green cells indicate a statistically significant better outcome (i.e., improvement); red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

3.2.8 SENSITIVITY ANALYSIS

- a) Influence of the funding source:* A recent meta-analysis of cardiovascular-related events among men taking testosterone replacement therapy reported that the risk of an event was higher in trials not funded by a pharmaceutical company than in those funded by a pharmaceutical company (4). Whether this apparent influence of the funding source extends to benefit outcomes is unknown. In this analysis, we included only data from trials that reporting having no industry funding. Trials that reported a mixture of industry and non-industry funding were excluded from this analysis, as were trials that did not report the funding source. Data were analyzed using the random-effects model, unless otherwise stated.
- b) Influence of bias:* In this analysis, we included only trials that we judged to be at low risk of bias, as determined by use of the Cochrane Risk of Bias tool. To be considered at low risk of bias for the purpose of this analysis, trials had to report adequate allocation concealment, adequate blinding (participants, outcome assessors, investigators) for subjective outcomes, and adequate consideration of incomplete data (completion over 80% and approximately equal in all arms). Criteria for high, low, and unclear risk of bias were based on the Cochrane Handbook for Systematic Reviews of Interventions. Data were analyzed using the random-effects model, unless otherwise stated.

3.2.9 SUBGROUP ANALYSIS

Subgroups were selected a priori in consultation with clinical experts to compare the benefits of testosterone replacement therapy across variants in the population for which a plausible difference in efficacy or safety may exist. The subgroups specified a priori were age ($< v. \geq 65$ yr), duration ($< v. \geq 6$ mo treatment), route of administration, and comorbidities (diabetes, depression, hypertension, obesity, coronary artery disease, hyperlipidemia). We classified trials as involving patients aged less than 65 years if the mean age plus 1 SD was below 65. We classified trials as involving patients aged 65 years or older if the mean age minus 1 SD was 65 or above. Assignment of a trial to a comorbidity subgroup was based on the eligibility criteria of each individual trial.

3.3 RESULTS

3.3.1 CHARACTERISTICS OF THE INCLUDED TRIALS

The initial search yielded 9149 reports, and 29 documents were retrieved through grey-literature searching (Figure 3.1). After duplicates were removed, 6169 records remained; the titles and abstracts of these records were assessed for potential inclusion. Of these, 321 records corresponded to conference abstracts. We evaluated the full-text of 868 articles, and 726 articles were excluded. In total, 142 publications were eligible for inclusion (Appendix 2). These publications corresponded to 70 unique RCTs and 38 unique non-randomized interventional studies (NRS-I). Records excluded at full-text review are listed in Appendix 4. In total, 321 conference abstracts were identified (Appendix 5). Abstracts were not formally excluded; however, no data were extracted. Data from non-randomized studies were not included in the analysis of benefits outcomes; harms data from non-randomized studies are summarized in Chapter 4.

Of the included RCTs, 7 were cross-over trials that did not report first-period data separately, and 6 included no outcomes of interest. One additional trial was included because it met our PICO statement; however, it did not report useable data (factorial trial of exercise and testosterone treatment. Data were reported for testosterone and no testosterone groups with no consideration of exercise component). Table 3.1 shows the characteristics of the 56 included RCTs that reported at least 1 outcome of interest. Eighteen trials reported no industry funding (32%), 10 (18%) reported a mixture of industry and non-industry funding, and 18 (32%) reported only industry funding sources. Ten trials (18%) did not report the source of funding. The included trials were published between 1997 and 2014, and the duration of treatment ranged from 3 months to 36 months (Table 3.2). The included populations were heterogeneous. For example, in some trials, the only criterion for inclusion was a low testosterone level (e.g., (19)). Others required symptoms of androgen deficiency (e.g., (20)) or a symptom score suggestive of androgen decline (e.g., (21)). Other trials, for example, included patients with chronic heart failure (22), diabetes (23), depression (24), or limited mobility or frailty (25).

FIGURE 3.1: SELECTION OF STUDIES FOR INCLUSION IN THE SYSTEMATIC REVIEW (PRISMA)

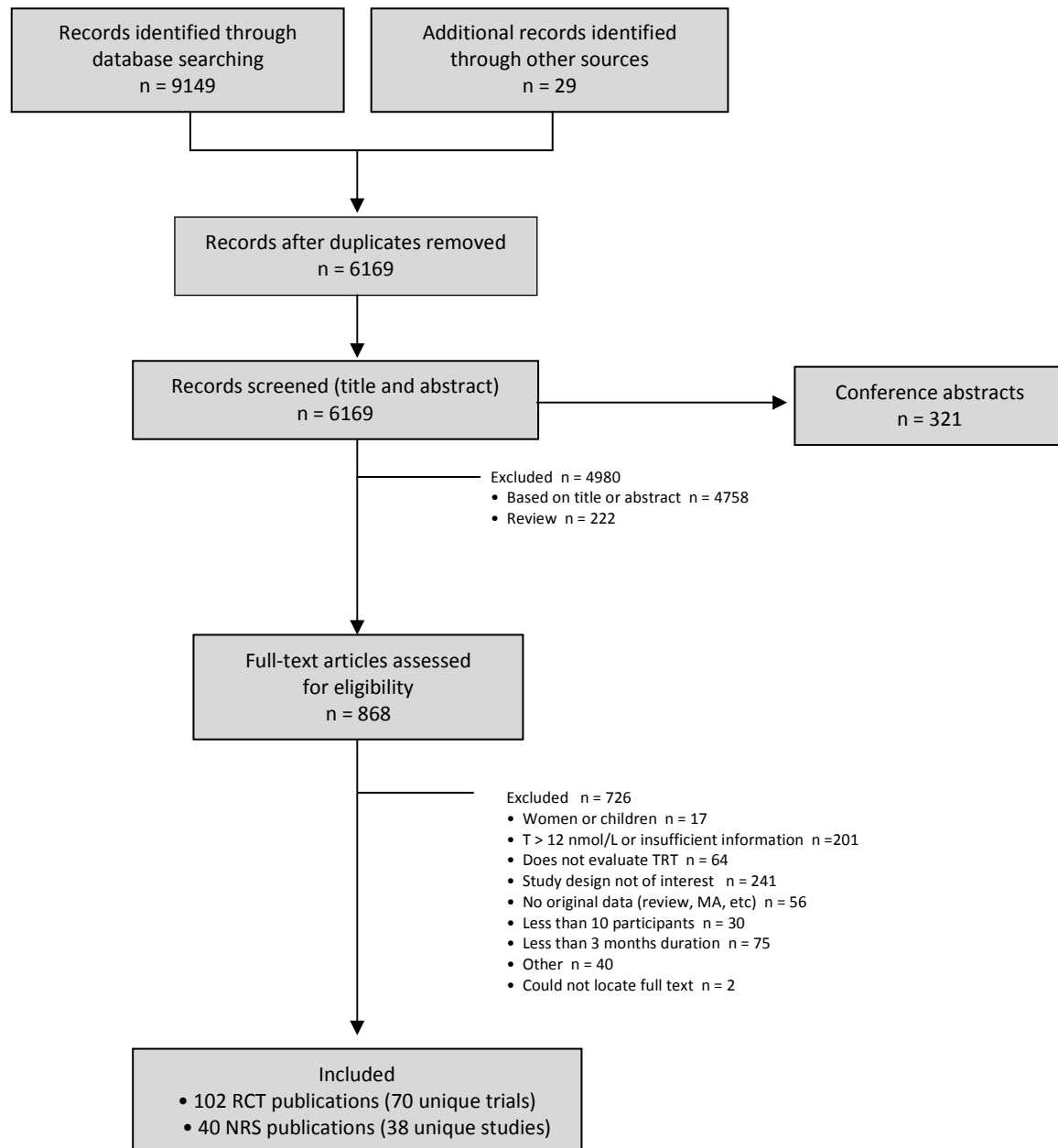


TABLE 3.1: CHARACTERISTICS OF INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Borst 2014, p. E433	Hypogonadal men	12 mo	Placebo (16) Delatestryl, IM, 125 mg/wk (14)	70.8 (9.7) 69.2 (8.0)	8.5 (10.1) 9.2 (11.9)	NR	Mix	US; NR	Factorial design: 2 arms involving Proscar were not included
Hackett 2013 p.1891 (Hackett 2013 p. 1612, Hackett 2014)	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) Nebido, IM, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	No	Yes	UK; multicentre	Cut-off point for “low” AMS score not specified; 16% with depression at baseline
Wang 2013, p. 1	Osteoporosis	24 mo	Placebo (62) Andriol, oral, 20 mg/d (62) Andriol, oral, 40 mg/d (62)	68.0 (4.8) 68.4 (5.5) 68.1 (5.4)	7.6 (0.7) 7.6 (0.9) 7.4 (0.8)	NR	No	China; NR	
Behre 2012, p. 198	AMS score >36	6 mo	Placebo (179) Testogel 1%, gel, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	10.6 (2.6) 10.4 (2.6)	Yes	Yes	Austria, Finland, Germany, Ireland, Italy, Spain, Sweden, UK	6 mo RCT followed by 6 mo observational study; data included only for RCT phase
Stout 2012, p. 893	Chronic heart failure	12 wk	Placebo (20) Sustanon, 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	NR	No	UK; single centre	Sustanon is a blend of T propionate, T phenylpropionate, T isocaproate, T decanoate
Spitzer 2012, p. 681 (Spitzer 2013)	Erectile dysfunction	14 wk	Placebo (70) Testim 1% gel, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	8.8 (2.4) 8.6 (2.2)	Yes	No	US; single centre	Sildenafil on demand permitted in both groups
Zhang 2012, p. 3806	Positive score on ADAM questionnaire	6 mo	Vitamin E/C (80) Andriol, oral, 120 or 160 mg/d (based on T level at baseline) (80)	61.1 (7.1) 59.4 (6.3)	7.7 (0.8) 8.0 (0.7)	No	No	China; single centre	Placebo was vitamin E/C capsules; “psychiatric diseases” were excluded; whether this includes patients with depression is not known.
Ho 2011, p. 260 (Tan 2013, Tong 2012)	At least mild AMS symptoms	42 wk	Placebo (60) Nebido, IM, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	8.9 (2) 9.1 (1.8)	NR	Yes	Malaysia; single centre	Nebido was injected at wk 0 and 6, followed by every 12 wk

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Jones 2011, p. 828 (Stanworth 2014)	MetS or T2D with at least 2 symptoms of hypogonadism	12 mo	Placebo (112) Tostran 2%, gel, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	9.5 (3.3) 9.2 (2.6)	Yes	Yes	Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, UK	
Kaufman 2011, p. 2079	Hypogonadal, "otherwise healthy"	6 mo	Placebo (40) AndroGel 1.62%, gel, 40.5 mg/d (234)	55.5 (10.3) 53.6 (9.5)	10.2 (NR) 9.8 (NR)	Yes	Yes	US; single centre	Open-label extension mentioned but not well reported; safety data not included
Sheffield-Moore 2011, p. E1831	Community-dwelling men	5 mo	Placebo (8) TE, IM, 100 mg/wk (8)	65 (3) 73 (8)	11.8 (2.9) 11.9(2.9)	Yes	No	US; single centre	Additional arm in which TE (100 mg/wk) was cycled monthly was not included in data analysis
Shigehara 2011, p. 53	Benign prostate hypertrophy	12 mo	No treatment (26) Eramone Depot, IM, 250 mg/4 wk (26)	68.9 (9.1) 72 (6.5)	Free T, pg/ml 6.7 (1.9) 7.0 (1.7)	NR	NR	Japan; single centre	No control treatment
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	Yes	NR	Italy; NR	Cross-over; first period (6 mo) included
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) Nebido, IM, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	NR	NR	Italy; single site	Trial was unblinded after 12 mo, and all received TRT onward; Nebido was injected at wk 0 and 6, followed by injections every 12 wk
Basaria 2010, p. 109 (Bachman 2014, Huang 2013, Basaria 2013, Travison 2011)	Limited mobility	6 mo	Placebo (103) Testim 1%, gel, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	Yes	No	US; multicentre	Trial stopped early by DSMB because of increased cardiovascular events in TRT arm
Kalinchenko 2010, p. 602 (Giltay 2010)	MetS	30 wk	Placebo (71) Nebido, IM, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	NR	Yes	Russia; NR	Age range 35-69 yr; Nebido was injected at wk 0 and 6, followed by injections every 12 wk

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Kenny 2010, p. 1134	Low bone mass and frailty	12–24 mo	Placebo (62) Androgel 1%, gel, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	NR	Mix	US; single site	I/E criteria was T < 350 ng/dL; Intended to be 24 mo but low recruitment; mean follow-up was 23 mo, but only 12 mo data presented for efficacy
Srinivas-Shankar 2010, p. 639 (O'Connell 2010, Atkinson 2010)	Intermediate-frail and frail	6 mo	Placebo (136) Testim 1% gel, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	Yes	Yes	UK; single-center study	
Caminiti 2009, p. 919 (Schwartz 2011)	Chronic heart failure	12 wk	Placebo (35) Nebido, IM, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	NR	No	Italy; single centre	Nebido was injected at wk 0, 6, and 12. Age was reported as median (IQR)
Chiang 2009, p. 467	Hypogonadal men	3 mo	Placebo (20) Androgel 1%, gel, 50 mg/d (20)	NR	NR	NR	NR	Taiwan; single centre	I/E criteria was total T ≤ 300 ng/dL
Emmelot-Vonk 2009, p. 129 (Emmelot-Vonk 2008, Nakhai-Pour 2007, Buisson 2010)	Moderately low T levels	26 wk	Placebo (117) Andriol, oral, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	NR	No	Netherlands; single centre	
Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16) Testogel, gel, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	NR	Yes	Germany; NR	Both groups received a diet and exercise intervention
Hohl 2009, p. 989	High AMS score	12 or 14 wk	Nebido, IM, 1000 mg/6 wk (10) Deposteron (TC), IM, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	9.9 (1.1) 10.1 (1.1) 9.9 (1.5)	NR	No	Brazil; single site	Nebido was injected at wk 0 and 6; Durateston is a blend of T propionate, T phenylpropionate, T isocaproate and T decanoate
Mathur 2009, p. 443	Chronic angina pectoris	12 mo	Placebo (7) Nebido, IM, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	NR	Yes	UK; NR	Nebido was injected at wk 0, 6, and 12
Morales 2009, p. 104	Sexual dysfunction	4 mo	Placebo (29) Androgel, oral, 160 mg/d (29)	60.2 (9.6) 59.0 (10.6)	10.0 (5.5) 10.2 (4.9)	NR	Yes	Canada; multicentre	Additional arm with DHEA treatment not included in analysis

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Shores 2009, p. 1009	Dysthymia or minor depression	12 wk	Placebo (16) Androgel 1%, gel, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	NR	Mix	US; single centre	12-wk RCT phase was followed by a 12-wk open-label extension phase (all patients received TRT); data not included in analysis
Agledahl 2008, p. 641	Subnormal total T	52 wk	Placebo (13) Nebido, IM, 1000 mg/12 wk (14)	69.3 (5.0) 68.9 (5.4)	8.2 (2.4) 8.5 (1.7)	NR	Mix	Norway; single centre	Nebido was injected at wk 0 and 6, followed by every 12 wk
Basurto 2008, p. 140	Low total T	12 mo	Placebo (23) TE, IM, 250 mg/3wk (25)	63.1 (7.7) 63.2 (8.5)	10.8 (1.3) 10.4 (1.1)	NR	No	Mexico; single centre	
Raynaud 2008, p. 168	Hypogonadal men	6 mo	Testopatch, patch, 4.8 mg/d (188) Androtardyl, IM, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	4.6 (3.2) 5.1 (3.3)	NR	Yes	France, Belgium, Germany, Netherlands, Spain	
Svartberg 2008, p. 378	NR	12 mo	Placebo (19) Nebido, IM, 1000 mg/12 wk (19)	69 (5) 69 (5)	8.2 (2.1) 8.4 (1.7)	NR	Mix	Norway; NR	Men selected as part of a prospective cohort study to participate in intervention study; Nebido was injected at wk 0 and 6, followed by every 12 wk
Chiang 2007, p. 411	Hypogonadal men	3 mo	Placebo (20) Androgel 1%, gel, 50 mg/d (20)	56.1 (14.6) 47.9 (17.0)	9.1 (6.9) 7.4 (5.6)	NR	Yes	Taiwan; multicentre	
Brockenbrough 2006, p. 251	Hemodialysis-dependent end-stage renal disease	6 mo	Placebo (21) Testim 1%, gel, 100 mg/d (19)	53.0 (17.2) 58.9 (14.9)	7.0 (3.0) 7.6 (2.2)	NR	Yes	US; single centre	
Marks 2006, p. 2351	Symptoms of late-onset hypogonadism	6 mo	Placebo (22) Delatestryl, IM, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	NR	Mix	US; single centre	Age was reported as median
Merza 2006, p. 381	Sexual dysfunction	6 mo	Placebo (19) Testoderm, patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	7.5 (2.5) 8.4 (3.3)	NR	Yes	UK; single centre	
Kuhnert 2005, p. 317	Primary, secondary, LOH and symptoms of T deficiency	24 wk	Androderm, patch, 5 mg/d (52) Testocur 2.5%, non-scrotal gel, 125 mg/d (56) Testocur 2.5%, scrotal gel, 25 mg/d (54)	53 (IQR 16) 52.2 (IQR 22.5) 50 (IQR 21)	NR	Yes	Yes	Germany; multicentre	I/E total T ≤ 10 nmol/L. Age was reported as median (IQR)

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Orengo 2005, p. 20	Treatment-resistant depression	12 wk	Placebo (5) Androgel 1%, gel, 50 mg/d (7)	63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	NR	No	US; single centre	Cross-over design; data extracted for first period for efficacy (safety data not provided by period)
Amory 2004, p. 503 (Page 2005, Vaughan 2007)	T below the range of normal for young adult men	36 mo	Placebo (24) TE, IM, 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	Yes	No	US; NR	Additional arm involving finasteride not included
Cavallini 2004, p. 641	Symptoms of androgen decline	6 mo	Placebo (45) TU, oral, 160 mg/d (40)	63 (NR) 64 (NR)	10.5 (2.1) 9.9 (1.8)	NR	No (*authors hold a patent on one of the treatments)	Italy; NR	Additional arm involving propionyl-L-carnitine not included
Schubert 2004, p. 5429 (Jockenhovel 2009, Jockenhovel 2009, Minnemann 2008)	Primary or secondary hypogonadism	30 wk	Nebido, 1000 mg/9 wk (20) Testosterone Depot (TE), IM, 250 mg/3 wk (20)	41.1 (13.4) 36.3 (12.3)	3.9 (4.4) 2.7 (2.3)	NR	Mix	Germany; NR	I/E cutoff was 5 nmol/L; Nebido was injected at wk 0 and 6 (3000 mg) followed by 1000 mg every 9 wks
Shabsigh 2004, p. 658 (Burnett 2013, Wang 2001, Swerdloff 2000)	Erectile dysfunction not responsive to sildenafil	12 wk	Placebo (36) Androgel 1%, gel, 50 mg/d (39)	59.1 (9.4) 56.8 (10.2)	65% had T < 10.4 (NR by group)	NR	Yes	US; multicentre	I/E for T level ≤ 400 ng/dl
Boyanov 2003, p. 1	T2DM, obesity, and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Andriol, oral, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	NR	NR	Bulgaria; single centre	No control treatment
McNicholas 2003, p. 69	≥ 1 symptoms of "low T"	90 d	Andropatch, patch, 5 mg/d (68) Testim 1%, gel, 50 mg/d (68) Testim 1%, gel, 100 mg/d (72)	57.9 (10.2) 59.0 (9.5) 56.7 (10.3)	7.90 (2.2) 7.95 (2.2) 7.92 (2.4)	NR	Yes	Denmark, Germany, Netherlands, Sweden, UK	
Steidle 2003, p. 2673 (Seftel 2004)	≥ 1 symptoms of "low T"	90 d	Placebo (99) Androderm, patch, 5 mg/d (102) Testim 1%, gel, 50 mg/d (99) Testim 1%, gel, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	7.9 (2.8) 8.3 (2.4) 8.1 (2.0) 8.1 (2.1)	Yes	Yes	US; multicentre	

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Tan 2003, p. 13	Alzheimer's disease	12 mo	Placebo (5) TE, IM, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	NR	No	US; single centre	"The 10 men selected for the study had "a total testosterone level ... < 10nmol/L"
Ferrando 2002, p. 358 (Ferrando 2003)	"Healthy older men"	6 mo	Placebo (5) TE 50–400 mg/wk (7)	67 (6.7) 68 (7.9)	9.8 (4.3) 12.4 (4.4)	Yes	No	US; single centre	Initial does of TE was 100 mg/wk; subsequent doses were based on T levels at the preceding visit and ranged from 50 mg to 400 mg
Kang 2002, p. 862	Coronary artery disease	12 wk	Placebo 17) Andriol, oral, 160 mg/d (18)	58 (9) 57 (7)	Free T, pg/ml 13.8 (1.8) 9.9 (3.1)	Yes	NR	South Korea; single centre	
Simon 2001, p. 2149	Healthy adult men	3 mo	Placebo (6) Testosterone gel, 125 mg/d (6)	55.4 (3.6) 52.8 (4.2)	9.4 (1.0) 8.3 (0.3)	Yes	NR	France; single centre	Third group not extracted: DHT gel, 35 mg/d
Bhasin 2000, p. 763	HIV-infected with weight loss	16 wk	Placebo (14) TE, IM, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	NR	No	US; multicentre	Factorial design, with exercise; exercise arms not included
Wang 2000, p. 2839	Primary, secondary or late-onset hypogonadism	90 d	Androderm, patch, 5 mg/d (76) Androderm, patch, 5 mg/d (76) Androderm, patch, 5 mg/d (76)	51.1 (NR) 51.3 (NR) 51.0 (NR)	8.2 (4.8) 8.2 (4.6) 8.6 (4.8)	Yes	Mix	US; multicentre	35%–45% had primary hypogonadism, 15%–25% had secondary hypogonadism
Clague 1999, p. 261	Community-living	3 mo	Placebo (7) TE, IM, 200 mg/2wk (7)	65.3 (1.8) 68.1 (6.6)	11.6 (0.9) 11.3 (1.7)	NR	No	UK; single centre	
Dobs 1999, p. 3469	Receiving TRT for at least 3 mo	24 wk	Androderm, patch, 5 mg/d (33) Delatestryl, IM, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	Yes	Mix	US, Sweden	
Bhasin 1998, p. 3155 (Arver 1999)	HIV	12 wk	Placebo (21) Androderm, patch, 5 mg/d (20)	NR	7.3 (2.9) 9.0 (1.7)	NR	Mix	US	TRT group: 40% aged > 40 yr; placebo group: 52% aged > 40 yr
Grinspoon 1998, p. 18 (Grinspoon 2000)	AIDS wasting syndrome	6 mo	Placebo (26) TE, IM, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	NR	No	US; single centre	
Jockenhovel 1997, p. 2510	Primary or secondary androgen deficiency	12 wk	Testoviron (TE), IM, 250 mg/3 wk (10) Testosterone pellets, 1200 mg (12)	30.0 (7.3) 36.3 (11.1)	1.6 (1.3) 1.9 (1.1)	NR	NR	Germany; NR	All pellets were inserted at day 1; I/E T cutoff 3.6 nmol/L

Author, year, page	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Dose adjustment permitted?	Industry funding	Country; no. of centres	Comments
Jockenhovel 1997, p. 293 (Jockenhovel 1999, Schubert 2001)	Primary or secondary androgen deficiency	210 d	Andriol, oral, 160 mg/d (13)	34.5 (14.1)	2.9 (1.4)	NR	NR	Germany; NR	All pellets were inserted at day 1; forth group was mesterolone (data not extracted)
			Testoviron, IM, 250 mg/3wk (15)	31.8 (10.1)	2.3 (2.3)				
			TestoImplant, pellets, 1200 mg (15)	35.8 (10.4)	2.7 (1.5)				
Sih 1997, p. 1661	Community-dwelling healthy men	12 mo	Placebo (15) TC, IM, 200 mg/2wk (17)	68 (6) 65 (7)	8.1 (0.7) 10.2 (0.9)	NR	NR	US; NR	
Note: ADAM = Androgen Deficiency in the Aging Male, AMS = Aging Male Symptoms scale, DHT = dihydrotestosterone, I/E = inclusion/exclusion, IM = intramuscular injection, IQR = interquartile range, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, T2DM = type 2 diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, WHO = World Health Organization. Studies included in the systematic review (met the I/E criteria) but reported no outcomes of interest: Cavallini 2012, Saeedi 2007, Montano 2007, Sullivan 2005, Lu 2003, Drinka 1995. Cross-over studies that did not report first-period data by treatment: Gopal 2010, Fennell 2010, Kapoor 2007, Kapoor 2006, Reid 1996, Tenover 1992, Handelsman 1990. Factorial design but data not provided according to study group: Hildreth 2013.									

TABLE 3.2: SUMMARY OF RANDOMIZED CONTROLLED TRIAL CHARACTERISTICS

Trial characteristic	Category	No. of included trials
Publication status	Literature sources	102
	Unique RCTs	70
	RCTs reporting useable data for least 1 outcome of interest	56
Country*	Canada	1
	US	21
	Other	34
Trial design*	Parallel	51
	Factorial	3
	Cross-over	2
Sponsors*	Industry	18
	Non-Pharmaceutical	18
	Mixed	10
	Not reported	10
Publication year*	--	1997 to 2014
No. randomized*	--	10 to 406

*Based on the included trials that reported at least 1 outcome of interest (n = 56)

3.3.2 RISK OF BIAS

The assessment of risk of bias using Cochrane's risk of bias tool showed that most trials were of low or unclear quality for the domains assessed (Table 3.3; Appendix 5). The overall risk of bias was generally high or unclear for most trials, primarily because of unclear or inadequate reporting of methods and analysis populations (Figure 3.2). In many trials, it was difficult to assess random sequence generation and allocation concealment because these characteristics were not well described. The method of blinding and who was blinded (e.g., investigator, outcome assessor, participants) were also not well reported. For objective outcomes (i.e., testosterone levels), we felt that this would not increase the risk of bias because of the use of laboratory measurements. However, for subjective outcomes (i.e., depression, quality of life, erectile function, libido), blinding was generally judged to be unclear or at high risk of bias because of inadequate detail provided in the published report or inappropriate blinding and the subjective nature of the outcome. In general, the reporting

of efficacy outcomes was poor (high or unclear risk of bias), and there were high rates of discontinuation that were variable across groups.

FIGURE 3.2: RISK OF BIAS SUMMARY FOR INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST

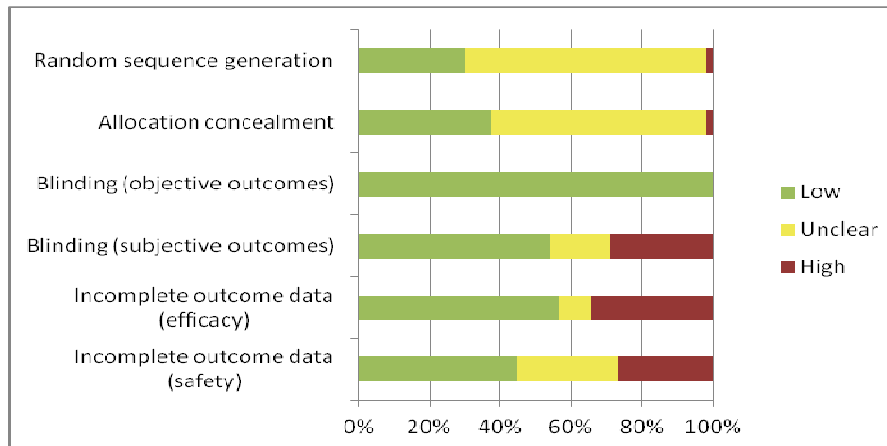


TABLE 3.3: RISK OF BIAS OF INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST

Author, year	Adequate sequence generation	Allocation concealment	Blinding of outcome assessment (objective outcomes)	Blinding of outcome assessment (subjective outcomes)	Incomplete outcome data addressed (efficacy outcomes)	Incomplete outcome data addressed (harm outcomes)
Borst 2014	Low	NR	Low	High	High	High
Hackett 2013	Unclear	Low	Low	Low	Low	Low
Wang 2013	Unclear	Unclear	Low	NA	Low	High
Behre 2012	Low	Low	Low	Low	Low	High
Spitzer 2012	Unclear	Low	Low	Low	Low	Low
Stout 2012	Unclear	Unclear	NA	Low	High	High
Zhang 2012	Unclear	Low	Low	High	Low	Low
Ho 2011	Unclear	Low	Low	Low	Low	Low
Jones 2011	Unclear	Unclear	Low	Low	High	High
Kaufman 2011	Unclear	Low	Low	Low	High	Low
Sheffield-Moore 2011	Unclear	Low	Low	NA	Low	High
Shigehara 2011	Unclear	Unclear	Low	High	Low	Low
Aversa 2010, p. 776	Unclear	Unclear	Low	Low	Unclear	Unclear
Aversa 2010, p. 3495	Unclear	Unclear	Low	Low	Low	Low
Basaria 2010	Low	Low	Low	Low	Low	Unclear
Kalinchenko 2010	Unclear	Low	Low	Low	Low	Low
Kenny 2010	Unclear	Low	Low	Low	High	Unclear
Srinivas-Shankar 2010	Low	Low	Low	Low	Low	Unclear

Caminiti 2009	Unclear	Low	Low	Low	Low	Low
Chiang 2009	Unclear	Unclear	Low	Low	High	High
Emmelot-Vonk 2009	Low	Low	Low	Low	Low	Low
Heufelder 2009	Low	Unclear	Low	High	Low	Low
Hohl 2009	High	High	Low	High	Low	Low
Mathur 2009	Low	Unclear	Low	Low	Low	High
Morales 2009	Low	Low	Low	Low	Low	Low
Shores 2009	Low	Low	Low	Low	High	Unclear
Agledahl 2008	Unclear	Unclear	Low	NA	Low	Low
Basurto 2008	Low	Low	Low	Low	Low	Unclear
Raynaud 2008	Unclear	Unclear	Low	High	High	High
Svartberg 2008	Unclear	Unclear	Low	Low	Low	Unclear
Chiang 2007	Unclear	Unclear	Low	Unclear	High	Low
Brockenbrough 2006	Unclear	Low	Low	Unclear	High	Low
Marks 2006						
Merza 2005	Unclear	Unclear	Low	Unclear	Low	Low
Kuhnert 2005	Unclear	Low	Low	High	High	High
Orengo 2005	Low	Unclear	Low	Unclear	High	High
Amory 2004	Low	Low	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Low	Unclear	Unclear	High
Schubert 2004	Low	Unclear	Low	High	Unclear	Low
Shabsigh 2004	Low	Unclear	Low	Low	Low	Unclear
Boyanov 2003	Unclear	Unclear	Low	High	Low	Low
McNicholas 2003	Unclear	Unclear	Low	High	High	High
Steidle 2003	Unclear	Unclear	Low	High	High	High
Tan 2003	Unclear	Unclear	Unclear	High	Low	Low
Ferrando 2002	Unclear	Unclear	Low	NA	Low	Low
Kang 2002	Unclear	Unclear	Low	NA	Low	Low
Simon 2001	Unclear	Unclear	Low	Low	NA	Low
Bhasin 2000	Low	Unclear	Low	Unclear	Low	Unclear
Wang 2000	Unclear	Unclear	Low	High	High	High
Clague 1999	Unclear	Unclear	Low	NA	Low	Low
Dobs 1999	Unclear	Low	Low	High	High	Unclear
Bhasin 1998	Unclear	Unclear	Low	Unclear	High	Unclear
Grinspoon 1998	Low	Low	Low	Low	High	Unclear
Jockenhovel 1997, p. 2510	Unclear	Unclear	Low	NA	Unclear	Unclear
Jockenhovel 1997, p. 293	Unclear	Unclear	Low	NA	Low	Unclear
Sih 1997	Low	Unclear	Low	Unclear	High	Unclear
Note: Risk of bias was not assessed for the studies that reported no outcome of interest or that did not provide usable data (e.g., cross-over studies with first period not reported separately).						

3.3.3 NETWORK META-ANALYSIS

We performed network meta-analyses for 5 outcomes: depression, quality of life, erectile function, libido, and total testosterone level. The number of participants ranged from 1057 to 4277 and involved up to 25 trials and 63 comparisons between treatments (Table 3.4). Most

trials were placebo-controlled trials with 2 arms. For each outcome, direct estimates (from randomized controlled trials) of efficacy were compared with mixed (direct plus indirect) estimates from the network meta-analysis.

TABLE 3.4: SUMMARY OF CHARACTERISTICS FOR EACH EVIDENCE NETWORK

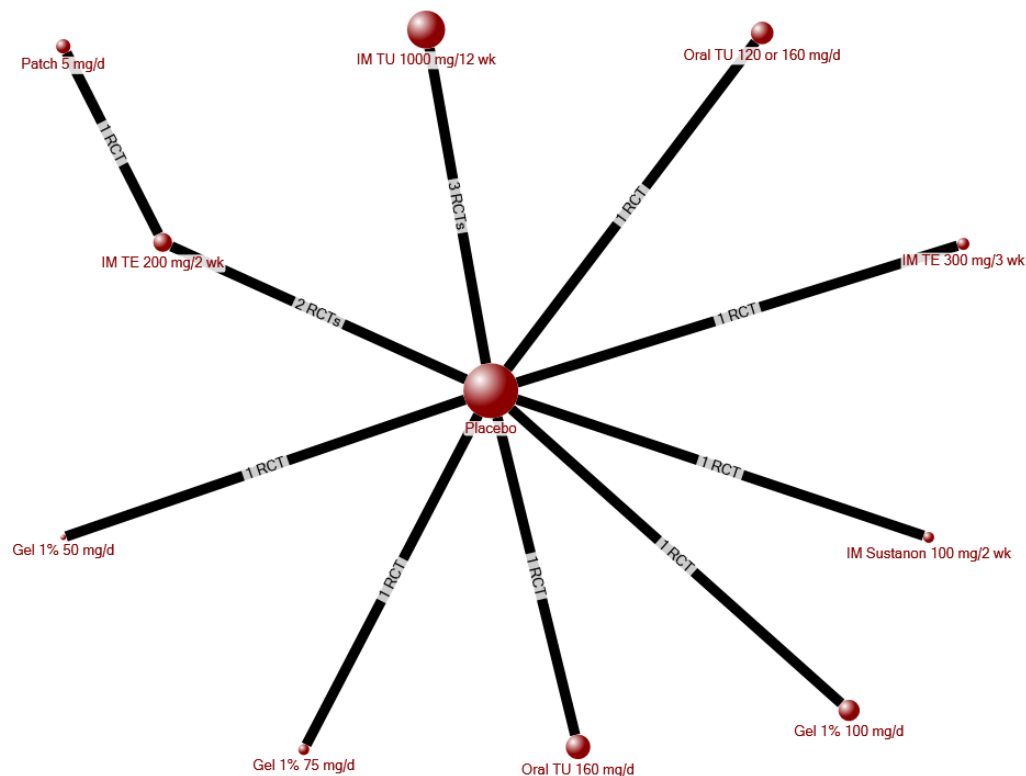
Characteristic	Testosterone level			Quality of life	Depression	Erectile function	Libido
	3 mo	6 mo	End of study				
No. of trials	23	19	46	20	12	10	10
No. of treatment nodes	15	17	25	14	10	5	7
No. of participants	2180	2095	4277	2610	1057	1138	1631
No. of comparisons	36	25	63	24	12	12	19
No. of 2-arm trials	18	16	39	18	12	9	7
No. of multi-arm trials	5	3	7	2	0	1	3

DEPRESSION

Twelve trials reported change in depressive symptoms as an outcome (13, 14, 19, 24, 26-33), all of which contributed to the evidence network (Table 3.5). Of the included trials, 2 enrolled patients with diagnosed depression at baseline (24, 32), and 3 included patients with symptoms of androgen deficiency (13, 14, 34). Most used the Beck Depression Inventory to assess the effect of testosterone on depressive symptoms (k = 6); others used the Hospital Anxiety and Depression Scale (HADS-D; k = 2), General Well-Being Index – Depressed Mood Dimension (k = 1), Hamilton Rating Scale for Depression (HAM-D; k = 3). In all but 1 scale (General Well-Being Index), a higher score indicated worse depression; the direction of the data based on this scale was reversed before analysis. The duration of the included trials ranged from 12 weeks to 3 years; however, only 1 trial lasted for more than 1 year (19).

The trials that informed the evidence network for depression included 1057 participants (Figure 3.8). Ten treatments were included in the network, providing 12 comparisons based on 12 trials each with 2 arms. Inconsistency could not be assessed in this network because of a lack of closed loops.

FIGURE 3.3: EVIDENCE NETWORK FOR DEPRESSION



In the network meta-analysis, 3 of 10 treatments were significantly better than placebo at resolving symptoms of depression: 2 treatments involved oral testosterone undecanoate (testosterone-based [T-based] dose [120 or 160 mg/d]; 160 mg/d) and 1 involved intramuscular injection of testosterone enanthate (200 mg/2 wk) (table 3.6). In the head-to-head comparisons, both oral testosterone undecanoate doses (160 mg/d T-based dose [120 or 160 mg/d]) were significantly better than most other treatments in the network at resolving symptoms of depression (Table 3.6, Table 3.7). The estimates from the mixed treatment analysis (incorporating indirect and direct evidence) were consistent with the estimates from the primary trials (direct evidence) (Table 3.8).

TABLE 3.5: CHARACTERISTICS OF TRIALS THAT ASSESSED DEPRESSION

Author, year	Population	Scale	Duration, wk	Treatment (no. randomized)	Age, mean (SD)	Score, mean (SD)		Significant in original study*	Industry funding	Comments
						Before	After			
Hackett 2013	T2DM and symptoms of hypogonadism	HADS-D	30	Placebo (102) IM TU 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	7.26 (4.10) 7.90 (3.91)	6.85 (4.10) 6.85 (3.91)	No	Yes	16% of patients had past or current depression; 12.5% were currently taking an antidepressant or had taken one in the last 6 mo
Stout 2012	Chronic heart failure	BDI	12	Placebo (20) Sustanon, 100 mg/2wk (20)	65.9 (8.8) 68.3 (5.3)	7.1 (5.2) 10.4 (8.7)	4.6 (3.4) 6.6 (3.8)	No	No	Antidepressant use NR
Spitzer 2012	Erectile dysfunction	General Well-Being Index, depressed mood domain†	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	86 (14.9) 86 (14.9)	83 (19) 85 (19)	No	No	Patients in both groups were also taking sildenafil; Antidepressant use NR
Zhang 2012	Positive score on ADAM questionnaire	HADS-D	26	Vitamin E/C (80) Oral TU, 120 or 160 mg/d† (80)	NR	4.82 (0.6) 4.91 (0.6)	4.29 (0.7) 2.39 (0.3)	Yes	No	Antidepressant use NR
Kalinchenko 2010	MetS	BDI	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.7) 51.6 (9.8)	9.1 (8.2) 9.7 (8.9)	7.2 (6.6) 6.1 (5.9)	No§	Yes	Patients with major depression taking antidepressants were excluded; 60% in each group had moderate to severe depressive symptoms
Shores 2009	Dysthymia or minor depression	HAM-D	12	Placebo (16) Gel 1%, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	13.8 (4.4) 12.7 (3.4)	11.4 (4.4) 8.4 (5.0)	No§	Mix	Men taking benzodiazepine or antipsychotics, substance dependence, schizophrenia, bipolar disorder, dementia or psychiatric instability or suicidality were excluded; 3 men in each group were on stable antidepressant dosages
Svartberg 2008	Elderly men	BDI	52	Placebo (19) IM TU, 1000 mg/12 wk (19)	69 (5) 69 (5)	4.8 (1.3) 5.1 (4.3)	4.3 (2.8) 3.8 (4.8)	No	Mix	Antidepressant use NR
Orengo 2005	Treatment-resistant depression	HAM-D	12	Placebo (5) Gel 1%, 50 mg/d (7)	63 (8.5) (NR by group)	16.2 (4.1) 15.4 (3.6)	9.4 (9.7) 9.4 (4.4)	No	No	All patients were taking antidepressants
Amory 2004	T below the range of normal for young	BDI	156	Placebo (24) IM TE, 200 mg/2 wk (24)	71 (4) 71 (4)	5.1 (1.0) 3.3 (0.6)	4.8 (1.0) 3.2 (0.6)	Yes	No	“Antidepressant use did not differ between

Author, year	Population	Scale	Duration, wk	Treatment (no. randomized)	Age, mean (SD)	Score, mean (SD)		Significant in original study*	Industry funding	Comments
						Before	After			
	adult men									treatment groups either at baseline (6 of 21 testosterone-treated vs. 2 of 18 placebo-treated patients"
Cavallini 2004	Symptoms of androgen decline	HDMS	26	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	7 (0.75)¶ 7 (0.75)¶	7 (0.75)¶ 5 (0.75)¶	Yes	No	Antidepressant use NR
Dobs 1999	Receiving TRT for at least 3 mo	BDI	24	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	4.8 (5.7) 4.7 (4.2)	3.9 (5.7) 4.9 (4.2)	No	Mix	Patients with clinically significant psychiatric disease, antidepressant use or antipsychotic therapy were excluded. 4 to 6 wk washout period was used before baseline.
Grinspoon 1998	AIDS wasting syndrome	BDI	26	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	13.4 (8.2) 15 (7.7)	10.8 (8.2) 9.2 (7.1)	No	No	Antidepressant use NR

Note: BDI = Beck Depression Inventory, ADAM = Androgen Deficiency in the Aging Male, HADS-D = Hospital Anxiety and Depression score, HAM-D = Hamilton Rating Scale for Depression, HDMS = Hamilton Depression and Melancholia Scale, depression domain, IM = intramuscular injection, MetS = metabolic syndrome, NR = not reported, SD = standard deviation, T2DM = type 2 diabetes mellitus, TE = testosterone enanthate, TU = testosterone undecanoate, T = testosterone, TRT = testosterone replacement therapy.

*Based on t test comparing mean of placebo and testosterone group at the end of treatment.

†Dose depended on T level at baseline.

‡Lower score indicates worse depression; direction of the data was reversed before analysis.

§Authors report significant after adjustment but rationale for adjustment not provided.

¶Data were reported as median (range). Median was assumed to be equal to mean for data analysis.

TABLE 3.6: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES

Standardized mean difference (standard deviation)											
Treatment	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Oral TU, T-based dose	Oral, TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 200 mg/3 wk	IM TE, 300 mg/3 wk	IM Sustanon, 100 mg/2 wk
Patch, 5 mg/d	−1.96 (1.28)	—									
Gel 1%, 50 mg/d	−0.02 (1.06)	1.94 (1.67)	—								
Gel 1%, 75 mg/d	−0.63 (0.93)	1.33 (1.59)	−0.61 (1.41)	—							
Gel 1%, 100 mg/d	−0.10 (0.89)	1.85 (1.57)	−0.09 (1.38)	0.52 (1.29)	—						
Oral TU, T-based dose [‡]	−3.52 [‡] (0.90)	−1.56 (1.59)	−3.50 [‡] (1.40)	−2.89 [‡] (1.31)	−3.41 [‡] (1.26)	—					
Oral TU, 160 mg/d	−2.64 [‡] (0.90)	−0.68 (1.59)	−2.63 [‡] (1.40)	−2.01 (1.31)	−2.54 [‡] (1.25)	0.88 (1.28)	—				
IM TU, 1000 mg/12 wk	−0.09 (0.53)	1.86 (1.39)	−0.08 (1.19)	0.53 (1.08)	0.01 (1.03)	3.42 [‡] (1.05)	2.55 [‡] (1.03)	—			
IM TE, 200 mg/2 wk	−1.76 [‡] (0.93)	0.20 (0.89)	−1.75 (1.43)	−1.13 (1.31)	−1.66 (1.28)	1.76 (1.31)	0.88 (1.29)	−1.67 (1.07)	—		
IM TE, 300 mg/3 wk	−0.20 (0.90)	1.76 (1.58)	−0.19 (1.40)	0.42 (1.30)	−0.10 (1.27)	3.32 [‡] (1.27)	2.44 (1.27) [‡]	−0.11 (1.04)	1.56 (1.30)	—	
IM Sustanon, 100 mg/2 wk [‡]	0.54 (0.94)	2.50 (1.60)	0.56 (1.41)	1.17 (1.32)	0.64 (1.29)	4.06 [‡] (1.30)	3.18 (1.32) [‡]	0.63 (1.08)	2.30 (1.33)	0.74 (1.30)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

*Oral TU dose was based on testosterone levels at baseline. Patients with total testosterone < 8 nmol/L received 120 mg/d; patients with testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose)

[‡]Sustanon is a blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

[‡]p < 0.05.

TABLE 3.7: DEPRESSION — HEAD-TO-HEAD COMPARISON OF THE TESTOSTERONE REPLACEMENT THERAPIES (VISUAL REPRESENTATION)

Treatment	1	2	2	4	5	6	7	8	9	10
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

Legend:

1. Patch, 5 mg/d	6. Oral TU, 160 mg/d
2. Gel 1%, 50 mg/d	7. IM TU, 1000 mg/12 wk
3. Gel 1%, 75 mg/d	8. IM TE, 200 mg/2 wk
4. Gel 1%, 100 mg/d	9. IM TE, 300 mg/3 wk
5. Oral TU, 120-160 mg/d	10. IM Sustanon, 100 mg/2 wk

Green cells indicate a statistically significant improvement of depression; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

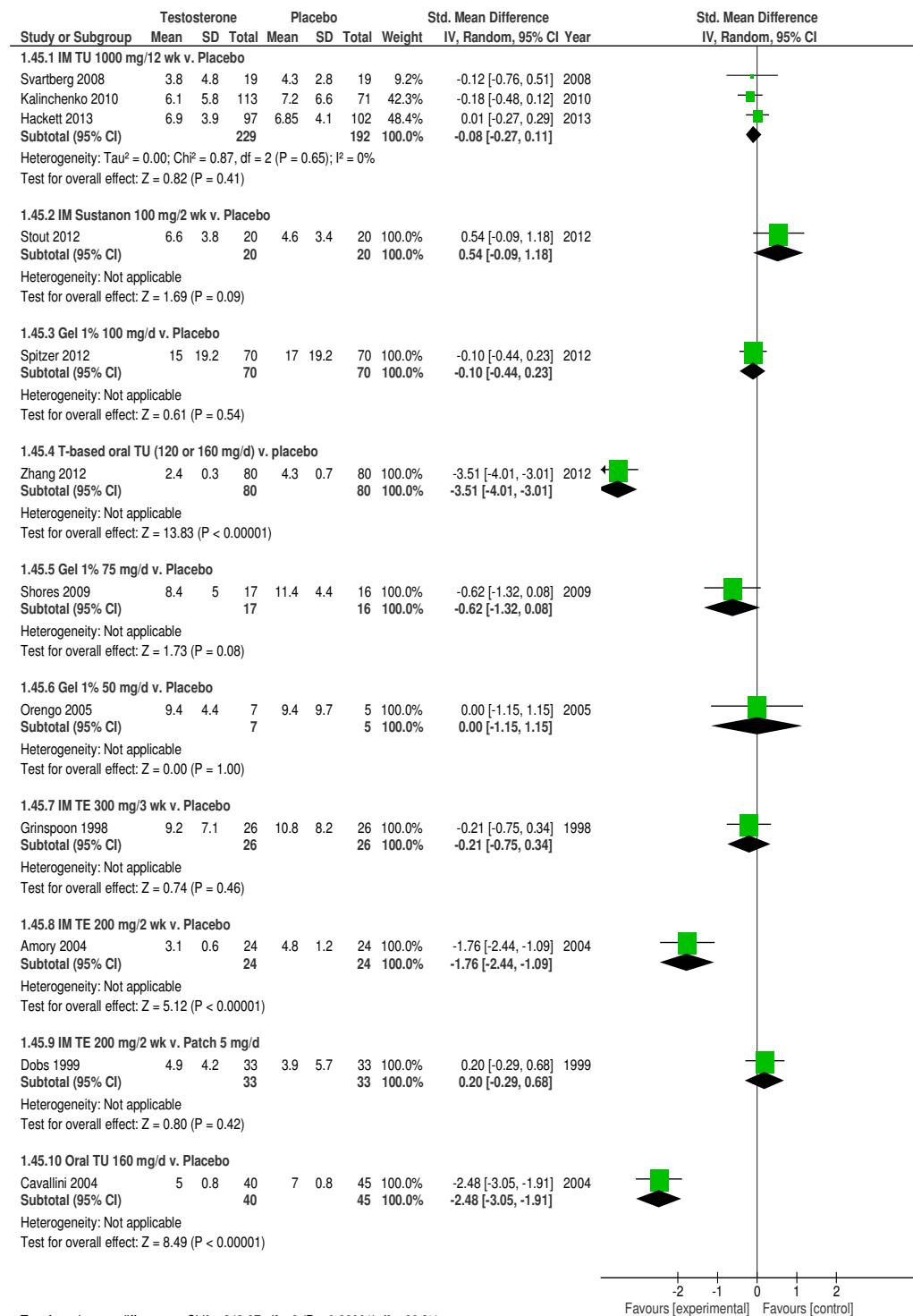
TABLE 3.8: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR DEPRESSION

Comparison		Direct evidence (primary studies)			Direct + indirect evidence (derived from NMA); SMD (95% CrI)	
		SMD (95% CI)	No. of studies	I^2 , %	Random-effects model	Fixed-effects model
Gel 1% 50 mg/d	Placebo	0.00 (-1.15 to 1.15)	1	NA	-0.02 (-1.90 to 1.86)	0.00 (-1.14 to 1.15)
Gel 1% 75 mg/d	Placebo	-0.62 (-1.32 to 0.08)	1	NA	-0.63 (-2.31 to 1.05)	-0.62 (-1.32 to 0.08)
Gel 1% 100 mg/d	Placebo	-0.10 (-0.44 to 0.23)	1	NA	-0.10 (-1.70 to 1.51)	-0.10 (-0.43 to 0.23)
T-based oral TU (120 or 160 mg/d)	Placebo	-3.51* (-4.01 to -3.01)	1	NA	-3.52* (-5.19 to -1.91)	-3.51* (-4.01 to -3.02)
Oral TU 160 mg/d	Placebo	-2.48* (-3.05 to -1.91)	1	NA	-2.64* (-4.30 to -1.00)	-2.64* (-3.23 to -2.06)
IM TU 1000 mg/12 wk	Placebo	-0.08 (-0.27 to 0.11)	3	0	-0.09 (-1.05 to 0.84)	-0.09 (-0.28 to 0.11)
IM TE 200 mg/2 wk	Placebo	-1.16* (-2.44 to -1.09)	1	NA	-1.76* (-3.42 to -0.04)	-1.77* (-2.44 to -1.10)
IM TE 300 mg/3 wk	Placebo	-0.21 (-0.75 to 0.34)	1	NA	-0.20 (-1.87 to 1.43)	-0.21 (-0.75 to 0.34)
IM Sustanon 100 mg/2 wk	Placebo	0.54 (-0.09 to 1.18)	1	NA	0.54 (-1.12 to 2.23)	0.54 (-0.09 to 1.17)
IM TE 200 mg/2wk	Patch 5 mg/d	0.20 (-0.29 to 0.68)	1	NA	0.20 (-1.42 to 1.83)	0.20 (-0.29 to 0.68)
				DIC	12.93	11.23
				Total residual deviance	11.29 (12 points)	10.76 (12 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, IM = intramuscular, NA = not applicable, NMA = network meta-analysis, SMD = standardized mean difference, TE = testosterone enanthate, TU = testosterone undecanoate.

* $p < 0.05$.

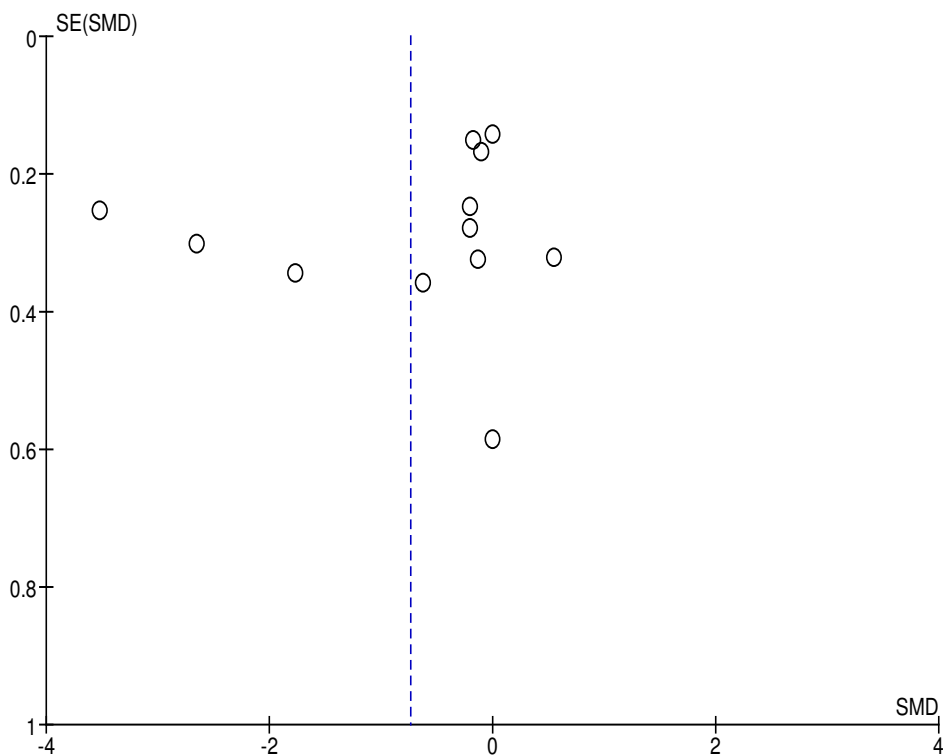
FIGURE 3.4: DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF TESTOSTERONE REPLACEMENT THERAPY ON DEPRESSIVE SYMPTOMS



PUBLICATION BIAS

The SE of the SMD was plotted against the SMD for each of the 12 included trials (Figure 3.5). Most of the trials reported a SMD close to zero, with the exception of the trials by Cavallini and colleagues (14), Zhang and colleagues (13), and Amory and colleagues (19). There were no small trials (large SE) that reported a positive SMD (indicating a negative effect of testosterone), suggesting potential publication bias.

FIGURE 3.5: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — DEPRESSION



SENSITIVITY ANALYSIS

INFLUENCE OF FUNDING

Of the 12 included trials for this outcome, 7 reported receiving no industry funding (13, 14, 19, 27, 28, 30, 32). The network involving trials with no industry funding included 7 treatments, giving 7 comparisons from 7 trials each with 2 arms. The total number of participants was 537. In this analysis, there were no significant differences between any of the included treatments and placebo or among the treatments. Of note, the 3 treatments that showed a significant effect on depressive symptoms in the primary analysis no longer showed a significant difference between placebo and testosterone replacement therapy among trials with no industry funding (Table 3.9) Some treatments could not be included in this analysis because they had not been evaluated in non-industry funded trials (patch 4 mg/d, 1% gel 75 mg/d, IM TU 1000 mg/d).

TABLE 3.9: DEPRESSION— HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS THAT REPORTED NO INDUSTRY FUNDING

Treatment	Standardized mean difference (standard deviation)							
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral, TU 160 mg/d	Oral TU, T-based dose*	IM TE, 200 mg/ 3 wk	IM TE, 300 mg/ 3 wk	IM Sustanon, 100 mg/ 2 wk
Gel 1%, 50 mg/d	0.01 (2.92)	—						
Gel 1%, 100 mg/d	−0.08 (2.87)	−0.08 (4.11)	—					
Oral TU, 160 mg/d	−2.64 (2.87)	−2.65 (4.10)	−2.57 (4.06)	—				
Oral TU, T-based dose*	−3.50 (2.87)	−3.51 (4.10)	−3.43 (4.08)	−0.86 (4.03)	—			
IM TE, 200 mg/2 wk	−1.77 (2.87)	−1.78 (4.11)	−1.70 (4.06)	0.87 (4.08)	1.73 (4.04)	—		
IM TE, 300 mg/3 wk	−0.20 (2.89)	−0.21 (4.10)	−0.12 (4.09)	2.45 (4.07)	3.30 (4.07)	1.58 (4.07)	—	
IM Sustanon,† 100 mg/2 wk	0.54 (2.89)	0.54 (4.10)	0.62 (4.06)	3.19 (4.09)	4.05 (4.09)	2.32 (4.06)	0.74 (4.08)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

*Oral TU dose was based on testosterone levels at baseline. Patients with total testosterone < 8 nmol/L received 120 mg/d; patients with testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

†Sustanon is a blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

RISK OF BIAS

Of the included trials for this outcome, 3 were considered to be at low overall risk of bias (low risk of bias for the domains allocation concealment, blinding [subjective outcomes], incomplete data addressed [efficacy outcomes]) (Table 3.10) and were included in our analysis (28, 29, 34).

The network for trials at low risk of bias included 2 treatments and 523 participants.

TABLE 3.10: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED DEPRESSION

Trial	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Hackett 2013	Low	Low	Low	Low
Stout 2012	Unclear	Low	High	High
Spitzer 2012	Low	Low	Low	Low
Zhang 2012	Low	High	Low	High
Kalinchenko 2010	Low	Low	Low	Low
Shores 2009	Low	Low	High	High
Svartberg 2008	Unclear	Low	Low	Unclear
Orengo 2005	Unclear	Unclear	High	High
Amory 2004	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Unclear	Unclear
Dobs 1999	Low	High	High	High
Grinspoon 1998	Low	Low	High	High

Compared with placebo, there was no significant difference in depressive symptoms following treatment with either 1% testosterone gel (100 mg/d) or intramuscular testosterone undecanoate (1000 mg/12 wk) (Table 3.11). There was no significant difference between the 2 treatments.

QUALITY OF LIFE

Twenty-one trials assessed quality of life among patients taking a testosterone replacement product (13, 21, 24, 26-29, 32, 35-45). One trial was excluded from the analysis because only mean change was reported (35). The duration of treatment was between 12 weeks and 1 year, although 7 trials (35%) involved treatment for less than 6 months (Table 3.12). Four

TABLE 3.11: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS

	Standardized mean difference (standard deviation)		
	Placebo	Gel 1%, 100 mg/d	IM TU 1000 mg/12 wk
Gel 1%, 100 mg/d	−0.10 (1.81)	—	
IM TU 1000 mg/12 wk	−0.09 (1.28)	0.01 (2.22)	—

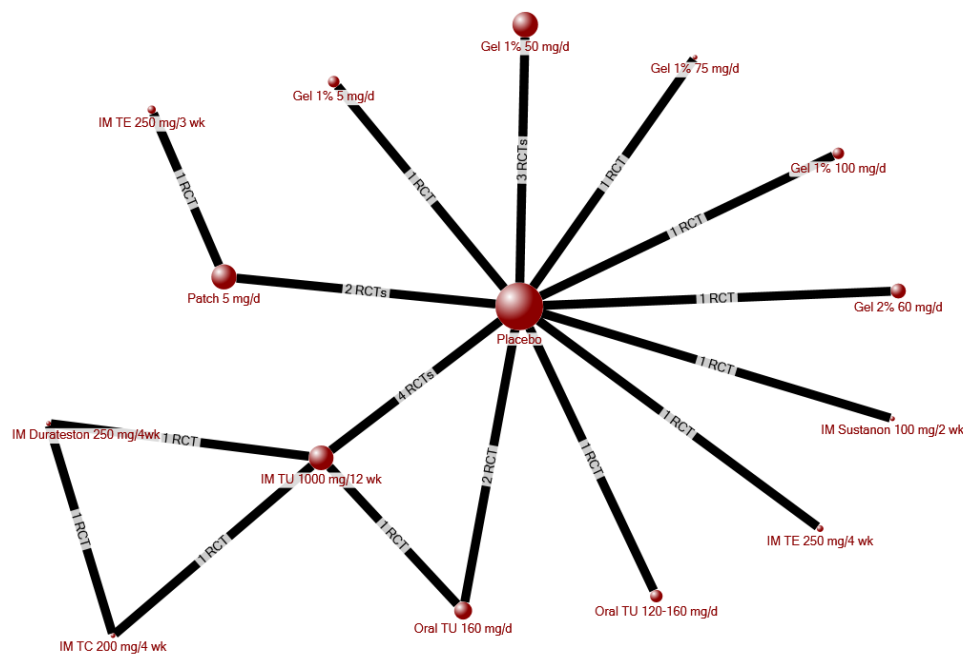
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

trials included participants with low quality of life (21, 34, 37, 46), and 2 recruited participants with symptoms of hypogonadism (13, 36). The remaining trials included a broad range of participants: depression (24, 32), sexual or erectile dysfunction (28, 41, 42), chronic heart failure (27), frailty (38, 40), diabetes or metabolic syndrome (29, 47), benign prostate hypertrophy (39), or HIV (44). Most trials assessed quality of life using the Aging Male Symptom scale (12 trials), in which a lower score indicates an improved quality of life. Six trials used a scale in which a higher score indicates improved quality of life; the direction of data for these trials was reversed before analysis.

The evidence network for quality of life included 20 trials with a total of 2610 participants. Overall, 14 treatments were compared, providing 24 comparisons based on 18 trials with 2 arms and 2 trials with 3 arms (Figure 3.6). Patch 4.8 mg/d was grouped with patch 5 mg/d to allow its inclusion in the network.

Compared with placebo, only 1 treatment (oral TU, T-based dose [120 or 160 mg/d]) significantly improved quality of life (SMD −1.96, SD 0.95). In the head-to-head comparisons, there were no significant differences between the treatments (Table 3.13).

FIGURE 3.6: EVIDENCE NETWORK FOR QUALITY OF LIFE



In the direct evidence (Table 3.14, Figure 3.7), several treatments appeared to improve quality of life; however, these differences were not conserved in the random-effects network meta-analysis model that incorporated indirect evidence. These treatments did show significant effects in the fixed effects model; however, based on DIC, total residual deviance, and heterogeneity of the included population, the random-effects model was considered to be a better fit for the data.

TABLE 3.12: CHARACTERISTICS OF TRIALS THAT ASSESSED QUALITY OF LIFE

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, mean, yr	Score, mean (SD)		Significant in original study**	Industry funding?
							Before	After		
Hackett 2013	T2DM and symptoms of hypogonadism	AMS	Higher score indicates worse QoL	30	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	40.17 (11.92) 42.33 (11.10)	37.31 (11.12) 37.14 (12.13)	No	Yes
Behre 2012	AMS score >36	AMS	Higher score indicates worse QoL	26	Placebo (179) Gel 1%, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	47.1 (8.0) 47.5 (9.5)	39.9 (9.4) 37.0 (10.8)	Yes	Yes
Stout 2012	Chronic heart failure	Minnesota Living with Heart Failure Questionnaire*	Higher score indicates worse QoL	12	Placebo (20) Sustanon, IM, 100 mg/2wk (20)	65.9 (8.8) 68.3 (5.3)	15.0 (15.2) 21.6 (13.6)	13.4 (10.0) 17.5 (10.9)	No	No
Spitzer 2012	Erectile dysfunction	MEDQoL	Higher score indicates improved QoL*	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	62 (25.6) 56 (27.4)	69 (25.6) 66 (27.7)	No	No
Zhang 2012	Positive score on ADAM questionnaire	AMS	Higher score indicates worse QoL	26	Placebo (80) Oral TU, 120 or 160 mg/d† (80)	NR	49.5 (9.5) 48.7 (10.1)	52.1 (10.3) 32.9 (9.2)	Yes	No
Ho 2011	At least mild AMS symptoms	AMS	Higher score indicates worse QoL	48	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	38.46 (11.85) 41.73 (12.73)	33.59 (10.69) 32.61 (9.67)	No	Yes
Jones 2011	MetS or T2DM ≥ 2 symptoms of hypogonadism	AMS	Higher score indicates worse QoL	52	Placebo (112) Gel 2%, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	39.9 (11.46) 40.6 (11.44)	37.8 (11.57) 36.4 (11.16)	No	Yes
Shigehara 2011	Benign prostate hypertrophy	AMS	Higher score indicates worse QoL	52	No treatment (26) IM TE, 250 mg/4 wk (26)	68.9 (9.1) 72.0 (6.5)	39.6 (8.6) 37.6 (10.4)	38.6 (7.7) 37.9 (8.3)	No	NR
Aversa 2010, p. 776	MetS or T2DM	AMS	Higher score indicates worse QoL	26	Placebo (10) Oral TU, 160 mg/d (10) IM TU, 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	37 (5) 38 (5) 38 (3)	36 (4) 36 (3) 29 (2)	• Placebo v. any TRT: yes • Placebo v. oral TRT: No • Placebo v. IM TRT: yes	NR
Kalinchenko 2010	MetS	AMS	Higher score indicates worse QoL	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.7) 51.6 (9.8)	42.3 (12.0) 44.3 (11.9)	37.6 (12.5) 32.2 (12.2)	Yes	Yes
Kenny 2010	Low bone mass and	IPSS, QoL domain	Higher score indicates worse	52	Placebo (62) Gel 1%, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	3.1 (1.3) 2.7 (1.3)	3.0 (1.5) 2.5 (1.3)	Yes	Mix

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, mean, yr	Score, mean (SD)		Significant in original study**	Industry funding?
							Before	After		
	physical frailty		QoL							
Srinivas-Shankar 2010	Intermediate-frail and frail	AMS, sexual function domain	Higher score indicates worse QoL	26	Placebo (136) Gel 1%, 50 mg/d (138)	73.7 (5.7) 73.9 (6.4)	13.8 (4.5) 13.7 (4.3)	12.3 (4.6) 10.9 (4.5)	Yes	Yes
Emmelot-Vonk 2009	Moderately low T levels	Questions on Life Satisfaction Modules, health domain	Higher score indicates improved QoL*	26	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	78.3 (34.2) 80.9 (28.2)	77.7 (30.7) 75.9 (28.7)	No	No
Hohl 2009	High AMS score	AMS	Higher score indicates worse QoL	14–16	IM TU, 1000 mg/6 wk (10) IM TC, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	35.3 (9.5) 36.7 (5.9) 40.5 (8.0)	23.8 (6.3) 28.2 (4.8) 29.6 (6.4)	• IM TU v. IM TC: No • IM TC v. Durateston: No • IM TU v. Durateston: No	No
Morales 2009	Sexual dysfunction	AMS	Higher score indicates worse QoL	16	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59 (10.6)	37.7 (8.3) 42.3 (10.2)	34.3 (13.3) 37.7 (10.7)	No	Yes
Shores 2009	Dysthymia or minor depression	Q-LES-Q	Higher score indicates improved QoL*	12	Placebo (16) Gel 1%, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	54.7 (13.5) 48.3 (10.4)	53.4 (13.7) 50.1 (11.1)	No	Mix
Raynaud 2008	Hypogonadal men	AMS	Higher score indicates worse QoL	53	Patch, 4.8 mg/d (188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	37.5 (0.9) 40 (2.5)	30 (1.1) 35 (2.5)	Yes	Yes
Merza 2006	Sexual dysfunction	MEDQoL	Higher score indicates improved QoL*	26	Placebo (19) Patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	54.2 (15.9) 61.4 (17.5)	43.6 (4.21) 61.8 (22.1)	Yes	Yes
Orengo 2005	Treatment-resistant depression	Q-LES-Q	Higher score indicates improved QoL*	12	Placebo (5) Gel 1%, 50 mg/d (7)	63 (8.5) (NR by group)	41.0 (7.2) 41.0 (7.1)	45.6 (12.5) 44.0 (7.1)	No	No
Bhasin 1998	HIV	HRQoL, sexual function domain	Higher score indicates improved QoL*	12	Placebo (21) Patch, 5 mg/d (20)	NR	63.1 (24.2) 76.2 (16.6)	77.3 (21.2) 87.4 (17.9)	No	Mix

Note: AMS = Aging Males' Symptoms, ADAM = Androgen Deficiency in the Aging Male, HRQoL = health-related quality of life, IM = intramuscular injection, IPSS = International Prostate Symptoms Scale, MEDQoL = Male Erectile Dysfunction-Specific Quality of Life, MetS = metabolic syndrome, NR = not reported, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, QoL = quality of life, T = testosterone, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*The direction of this scale was reversed before analysis.

†Dose of oral TU depended on baseline total T level. Patients with total T < 8 nmol/L received 160 mg/d; patients with total T between 8 and 12 nmol/L received 120 mg/d.

TABLE 3.13: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES

	Standardized mean difference (standard deviation)*														
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	TU, oral, 160 mg/d	Oral TU, T-based dose†	IM TU, 1000 mg/12 wk	IM TE, 250 mg/3 wk	IM TE, 250 mg/4 wk	IM TC, 200 mg/4 wk	IM Sustanon, 100 mg/2 wk	IM Durateston, 250 mg/4 wk
Patch, 5 mg/d	-0.80 (0.70)	—													
Gel 1%, 5 mg/d	-0.35 (0.94)	0.45 (1.17)	—												
Gel 1%, 50 mg/d	-0.19 (0.57)	0.61 (0.90)	0.16 (1.10)	—											
Gel 1%, 75 mg/d	0.26 (1.00)	1.06 (1.22)	0.61 (1.38)	0.45 (1.15)	—										
Gel 1%, 100 mg/d	-0.04 (0.95)	0.76 (1.18)	0.32 (1.34)	0.15 (1.11)	-0.30 (1.38)	—									
Gel 2%, 60 mg/d	-0.12 (0.94)	0.68 (1.18)	0.23 (1.33)	0.06 (1.10)	-0.39 (1.37)	-0.09 (1.34)	—								
Oral TU, 160 mg/d	0.25 (0.55)	1.05 (0.89)	0.60 (1.09)	0.44 (0.79)	0.01 (1.14)	0.29 (1.09)	0.37 (1.09)	—							
Oral TU, T-based dose†	-1.96† (0.95)	-1.05 (0.89)	-1.61 (1.34)	-1.77 (1.11)	-2.22 (1.38)	-1.93 (1.34)	-1.84 (1.33)	-2.21 (1.10)	—						
IM TU, 1000 mg/12 wk	-0.77 (0.48)	-0.03 (0.85)	-0.42 (1.06)	-0.58 (0.75)	-1.03 (1.11)	-0.74 (1.06)	-0.65 (1.06)	-1.02 (0.67)	1.19 (1.06)	—					
IM TE, 250 mg/3 wk	-0.47 (1.48)	0.33 (0.95)	-0.12 (1.51)	-0.28 (1.31)	-0.73 (1.55)	-0.44 (1.52)	-0.34 (1.51)	-0.72 (1.30)	1.49 (1.51)	0.30 (1.28)	—				
IM TE, 250 mg/4 wk	-0.09 (0.97)	0.71 (1.20)	0.27 (1.35)	0.10 (1.13)	-0.35 (1.40)	-0.05 (1.35)	0.04 (1.35)	-0.34 (1.12)	1.88 (1.36)	0.69 (1.09)	0.38 (1.53)	—			
IM TC, 200 mg/4 wk	-0.02 (1.14)	0.78 (1.34)	0.34 (1.48)	0.17 (1.27)	-0.28 (1.52)	-0.02 (1.48)	-0.11 (1.48)	-0.27 (1.23)	1.94 (1.48)	0.76 (1.03)	0.45 (1.65)	-0.07 (1.50)	—		
IM Sustanon, 100 mg/2 wk	0.39 (0.99)	1.19 (1.21)	0.74 (1.36)	0.58 (1.14)	0.13 (1.41)	0.42 (1.36)	0.51 (1.37)	0.14 (1.13)	2.35 (1.36)	1.16 (1.10)	0.86 (1.53)	0.47 (1.39)	0.40 (1.51)	—	
IM Durateston 250 mg/4wk	-0.02 (1.14)	0.78 (1.33)	0.33 (1.48)	0.17 (1.27)	-0.28 (1.51)	-0.01 (1.48)	0.10 (1.47)	-0.27 (1.23)	1.94 (1.48)	0.75 (1.03)	0.45 (1.64)	0.06 (1.50)	0.00 (0.104)	-0.41 (1.51)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model.

†Oral TU dose was based on testosterone levels at baseline. Patients with total T < 8 nmol/L received 120 mg/d; patients with T between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

‡p < 0.05.

TABLE 3.14: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR QUALITY OF LIFE

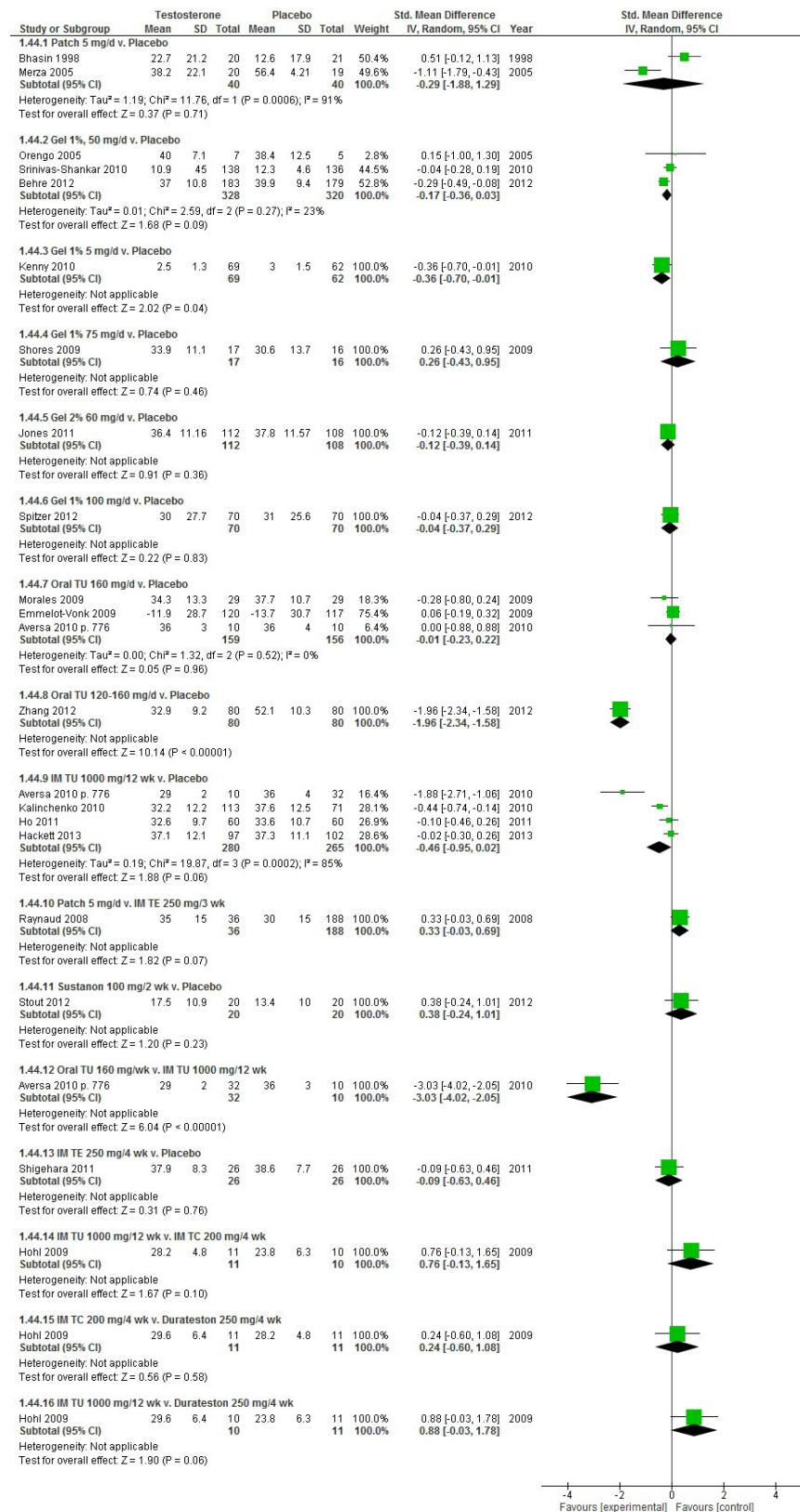
Comparison		Direct evidence			Direct + indirect evidence (derived from NMA); SMD (95% CrI)	
		SMD (95% CI)	No. of studies	I^2 , %	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	-0.29 (-1.88 to 1.29)	2	91	-0.81 (-2.20 to 0.60)	-0.78* (-1.24 to -0.33)
Gel 1% 5 mg/d	Placebo	-0.36* (-0.70 to -0.01)	1	NA	-0.35 (-2.25 to 1.55)	-0.35* (-0.70 to -0.01)
Gel 1% 50 mg/d	Placebo	-0.17 (-0.36 to 0.03)	3	23	-0.19 (-1.30 to 0.96)	-0.29* (-0.44 to -0.13)
Gel 1% 75 mg/d	Placebo	0.26 (-0.43 to 0.95)	1	NA	0.26 (-1.74 to 2.26)	0.26 (-0.43 to 0.95)
Gel 1% 100 mg/d	Placebo	-0.04 (-0.37 to 0.29)	1	NA	-0.04 (-1.95 to 1.89)	-0.04 (-0.37 to 0.29)
Gel 2% 60 mg/d	Placebo	-0.12 (-0.39 to 0.14)	1	NA	-0.12 (-2.03 to 1.78)	-0.12 (-0.39 to 0.14)
Oral TU 160 mg/d	Placebo	-0.01 (-0.23 to 0.22)	3	0	0.25 (-0.84 to 1.35)	0.08 (-0.14 to 0.30)
Oral TU T-based dose (120 or 160 mg/d)†	Placebo	-1.96* (-2.34 to -1.58)	1	NA	-1.96 (-3.86 to -0.04)	-1.96* (-2.34 to -1.58)
IM TU 1000 mg/d	Placebo	-0.62* (-1.22 to -0.01)	4	90	-0.77 (-1.79 to 0.14)	-0.30 (-0.47 to -0.12)*
Sustanon 100 mg/wk	Placebo	0.38 (-0.24 to 1.01)	1	NA	0.39 (-1.60 to 2.36)	0.38 (-0.24 to 1.01)
IM TE 250 mg/4 wk	Placebo	-0.09 (-0.63 to 0.46)	1	NA	-0.09 (-2.05 to 1.87)	-0.09 (-0.63 to 0.46)
IM TE 250 mg/3wk	Patch 5 mg/d	0.33 (-0.03 to 0.69)	1	NA	0.33 (-1.58 to 2.25)	0.33 (-0.03 to 0.69)
IM TU 1000 mg/12 wk	Oral TU 160 mg/wk	-3.03* (-4.02 to -2.05)	1	NA	-1.02 (-2.42 to 0.25)	-0.38* (-0.66 to -0.11)
IM TC 200 mg/4 wk	IM TU 1000 mg/12 wk	0.76 (-0.13 to 1.65)	1	NA	0.76 (-1.32 to 2.82)	0.76 (-0.15 to 1.65)
IM TC 200 mg/4 wk	Durateston 250 mg/4 wk	0.24 (-0.60 to 1.08)	1	NA	0.00 (-2.07 to 2.06)	0.00 (-0.89 to 0.90)
Durateston 250 mg/4 wk	IM TU 1000 mg/12 wk	0.88 (-0.03 to 1.78)	1	NA	0.75 (-0.30 to 2.82)	0.76 (-0.13 to 1.64)
				DIC	21.52	47.55
				Total residual deviance	23.22 (20 points)	56.67 (20 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criterion, IM = intramuscular injection, NA = not applicable, NMA = network meta-analysis, SMD = standardized mean difference, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

* $p < 0.05$.

†Oral TU dose was based on testosterone levels at baseline. Patients with total T < 8 nmol/L received 120 mg/d; patients with T between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

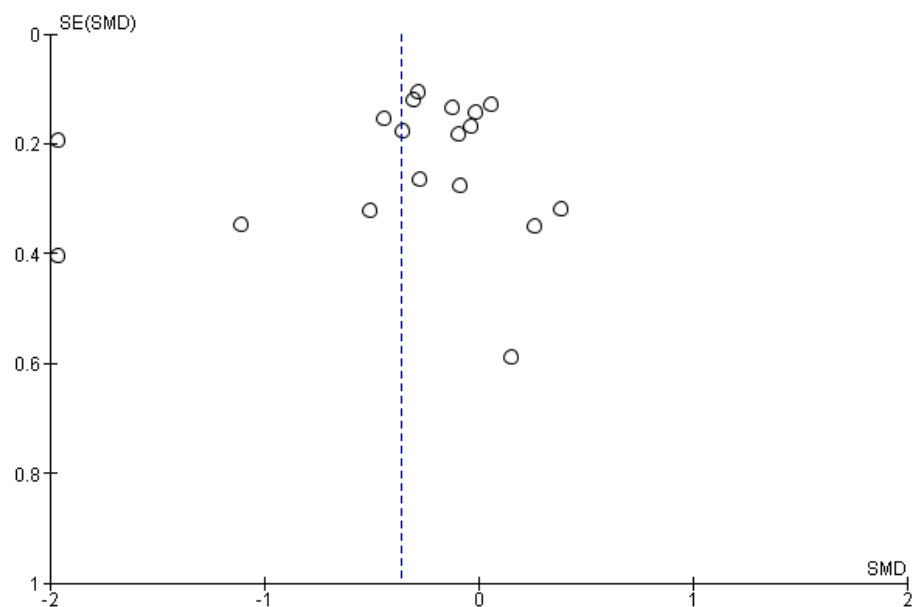
FIGURE 3.7: DIRECT EVIDENCE FOR QUALITY OF LIFE



PUBLICATION BIAS

Of the 20 included trials, 18 involved 2 treatment arms and were included in the funnel plot for the assessment of publication bias (Figure 3.8). The SMD for most trials was close to zero, and most had a small SE. There were few trials that had a large SE, and no trials with a large SE and either a positive or negative SMD, suggesting that most trials found no difference in quality of life, regardless of the number of participants. This suggests that the potential for publication bias is low.

FIGURE 3.8: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — QUALITY OF LIFE



SENSITIVITY ANALYSES

INFLUENCE OF FUNDING

Of the 20 included trials, 6 reported having no industry funding (13, 27, 28, 32, 45, 46). The trial by Hohl and colleagues (46) was omitted from the network analysis because it did not connect through a common comparator (IM TU 1000 mg/12 wk v. IM TC 200 mg/4 wk v. IM Durateston 250 mg/4 wk). Hohl and colleagues (46) reported no significant difference between treatment groups in score on the AMS scale.

The network involving trials with no industry funding included 5 treatments, giving 5 comparisons from 5 trials each with 2 arms. The number of included participants was 589. In this analysis, there were no significant differences in outcome between any of the treatments and placebo, or among the treatments. The 1 treatment that showed a significant effect in the primary analysis (oral TU, T-based dose [120 or 160 mg/d]) had no significant effect on quality of life relative to placebo when only trials with no industry funding were included in the analysis (Table 3.15).

TABLE 3.15: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS THAT REPORTED NO INDUSTRY FUNDING

	Standardized mean difference (standard deviation)*					
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	TU, oral, 160 mg/d	Oral TU, T-based dose†	IM Sustanon, 100 mg/2 wk
Gel 1%, 50 mg/d	0.13 (2.90)	—				
Gel 1%, 100 mg/d	−0.03 (2.86)	−0.16 (4.07)	—			
Oral TU, 160 mg/d	0.04 (2.85)	−0.09 (4.06)	0.07 (4.05)	—		
Oral TU, T-based dose†	−1.96 (2.85)	−2.09 (4.05)	−1.93 (4.04)	−2.00 (4.03)	—	
IM Sustanon, 100 mg/2 wk	0.37 (2.86)	0.24 (4.06)	0.40 (4.03)	0.33 (4.04)	2.33 (4.04)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.
 *Random-effects model.
 †Oral TU dose was based on testosterone levels at baseline. Patients with total testosterone 8 nmol/L received 120 mg/d; patients with testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

RISK OF BIAS

Of the included trials, 9 were judged to be at overall low risk of bias (21, 28, 29, 34, 37, 40-42, 45) (Table 3.16). The evidence network for quality of life based on trials at low risk of bias included 1613 participants and 5 treatments. Nine comparisons were made, based on 9 trials, each with 2 arms.

TABLE 3.16: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED QUALITY OF LIFE

Trial	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Hackett 2013	Low	Low	Low	Low
Stout 2012	Unclear	Low	High	High
Spitzer 2012	Low	Low	Low	Low
Behre 2012	Low	Low	Low	Low
Zhang 2012	Low	High	Low	High
Ho 2012	Low	Low	Low	Low
Jones 2011	Unclear	Low	High	High
Shigehara 2011	Unclear	High	Low	High
Aversa 2010, p. 776	Unclear	Low	Unclear	Unclear
Kalinchenko 2010	Low	Low	Low	Low
Kenny 2010	Low	Low	High	High
Srinivas-Shankar 2010	Low	Low	Low	Low
Hohl 2009	High	High	Low	High
Morales 2009	Low	Low	Low	Low
Shores 2009	Low	Low	High	High
Emmelot-Vonk 2009	Low	Low	Low	Low
Raynaud 2008	Unclear	High	High	High
Merza 2005	Unclear	Unclear	Low	Low
Orengo 2005	Unclear	Unclear	High	High
Bhasin 1998	Unclear	Unclear	High	High

When only trials at low risk of bias were included in the analysis, patch 5 mg/d was associated with a significant improvement in quality of life relative to placebo (Table 3.17). There were no significant difference between placebo and any of the other testosterone replacement products included in this network. In the head-to-head comparisons, patch 5 mg/d was significantly better than testosterone gel (50 mg/d) and oral testosterone undecanoate (160 mg/d) at improving quality of life.

ERECTILE FUNCTION

Fourteen trials reported erectile function as an outcome (14, 26, 28, 29, 35-37, 41, 45, 47-51). Four trials were not included in the network meta-analysis: 1 reported dichotomous outcomes based on International Index of Erectile Function (IIEF) score (35), 1 reported a

TABLE 3.17: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS

	Standardized mean difference (standard deviation)*					
	Placebo	Patch 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU 1000 mg/12 wk
Patch 5 mg/d	−1.10 (0.46)†	—				
Gel 1%, 50 mg/d	−0.29 (0.23)	0.80 (0.51)	—			
Gel 1%, 100 mg/d	−0.04 (0.35)	1.06 (0.57)†	0.25 (0.41)	—		
Oral TU, 160 mg/d	−0.05 (0.25)	1.05 (0.52)†	0.25 (0.34)	−0.01 (0.43)	—	
IM TU 1000 mg/12 wk	−0.19 (0.19)	0.91 (0.49)	0.11 (0.30)	−0.15 (0.39)	−0.14 (0.32)	—
Note: IM = intramuscular injection, TU = testosterone undecanoate. *Random-effects model. † $p < 0.05$.						

dichotomous outcome of “ever” v. “never” for difficulty in achieving an erection (45), and 1 assessed the frequency of nocturnal erections (51). One trial was excluded because the data presented in the table and text were not consistent with the description in the methods section. Boyanov and colleagues (50) stated that they assessed erectile function using the IIEF-5; however, their data and interpretation were inconsistent with the use of this scale. The characteristics of the included trials are shown in Table 3.18.

The treatment duration of the included trials ranged from 12 weeks to 1 year (Table 3.18). Of the trials included in the network, all assessed erectile function using a version of the IIEF scale: 8 used the erectile function domain of IIEF, while 2 used IIEF-5, which is simplified version of IIEF targeted toward erectile function. A higher score indicates improved erectile function for both IIEF and IIEF-5. Of the included trials, the target population was men with sexual dysfunction in 2 studies (28, 41). The remaining trials enrolled men with symptoms of hypogonadism (14, 34, 36, 37), diabetes or metabolic syndrome (29, 47), or with low testosterone only (48, 49).

TABLE 3.18: CHARACTERISTICS OF TRIALS THAT ASSESSED ERECTILE FUNCTION

Trial	Population	Scale	Direction of scale*	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study†	Industry funding	Comments
							Before	After			
Hackett 2013	T2DM and symptoms of hypogonadism	IIEF, EF domain	Higher score indicates improved function	30	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	11.64 (10.05) 13.24 (9.80)	10.52 (10.43) 13.99 (10.89)	Yes	Yes	ED at baseline: 84% based on an IIEF score of 25 or less; 16% were taking a PDE5 inhibitor; more men in the placebo group than in the active group were taking a PDE5 inhibitor (18% v. 8%)
Spitzer 2012	Erectile dysfunction	IIEF, EF domain	Higher score indicates improved function	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	20 (8.5) 19 (8.5)	19 (14.9) 21 (8.5)	No	No	All men had ED at baseline; Patients in both groups were taking sildenafil on demand
Ho 2011	At least mild AMS symptoms	IIEF-5	Higher score indicates improved function	48	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	15.55 (5.8) 14.3 (6.2)	16.5 (6.0) 16.5 (5.9)	No	Yes	ED at baseline: 24% Placebo group; 18% TRT group; ED medication use not reported
Jones 2011	MetS or T2DM with at least 2 symptoms of hypogonadism	IIEF, EF domain	Higher score indicates improved function	52	Placebo (112) Gel 2%, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	11.9 (10.0) 12.0 (9.1)	14.4 (10.4) 15.2 (9.7)	No	Yes	Prevalence of ED at baseline not reported; PDE-5 inhibitor use allowed
Aversa 2010 (p. 776)	MetS or T2DM	IIEF-5	Higher score indicates improved function	26	Placebo (10) Oral TU, 160 mg/d (10) IM TU, 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	16 (2) 17 (3) 17 (2)	19 (4) 18 (3) 20 (3)	• IM TRT v. placebo: No • Oral TRT v. placebo: No • Oral TRT v. placebo: No	NR	ED at baseline: 60% Placebo, 75% IM TRT; rate of ED medication use not reported; however, “Almost all patients in our study abandoned the use of [PDE-5] inhibitors for enhancing their erectile function within 6 months of IM TU treatment ... in contrast to those in the oral TU and P arms.”
Kalinchenko 2010	MetS	IIEF-5	Higher score indicates improved function	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	14.1 (7.3) 13.0 (7.3)	14.5 (7.3) 16.5 (7.3)	No	Yes	Prevalence of ED and ED medication use not reported at baseline not reported
Chiang 2009	Hypogonadal men	IIEF-15, EF domain	Higher score indicates improved function	12	Placebo (20) Gel 1%, 50 mg/d (20)	NR	16.9 (8.2) 13.3 (6.8)	15.3 (8.2) 20.6 (6.8)	Yes	NR	Prevalence of ED at baseline not reported; no patient had ever used PDE inhibitors or any type of treatment for SD

Trial	Population	Scale	Direction of scale*	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study†	Industry funding	Comments
							Before	After			
Morales 2009	SD	IIEF, EF domain	Higher score indicates improved function	16	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6)	10.4 (8.3)	11.3 (9.1)	No		Inclusion criteria: > 3-mo history of SD (IIEF score < 25 on questions 1–5 and 15)
						59.0 (10.6)	11.5 (7.0)	11.1 (7.7)			
Chiang 2007	Hypogonadal men	IIEF-15, EF domain	Higher score indicates improved function	12	Placebo (20) Gel 1%, 50 mg/d (20)	56.1 (14.6)	16.9 (9.6)	18.1 (10.7)	No		ED medication use not reported
						47.9 (17.0)	15.8 (9.5)	21.6 (6.8)			
Cavallini 2004	Symptoms of androgen decline	IIEF, EF domain	Higher score indicates improved function	26	Placebo (45) Oral TU, 160 mg/d	63 (NR)	8 (4.0)‡	9 (4)‡	Yes		
						64 (NR)	8 (3.5)‡	16 (5.8)‡			

Note: EF = erectile function, IIEF = International index of erectile function, MetS = metabolic syndrome, NR = not reported, SD = sexual dysfunction, T2DM = type 2 diabetes mellitus, TU = testosterone undecanoate.

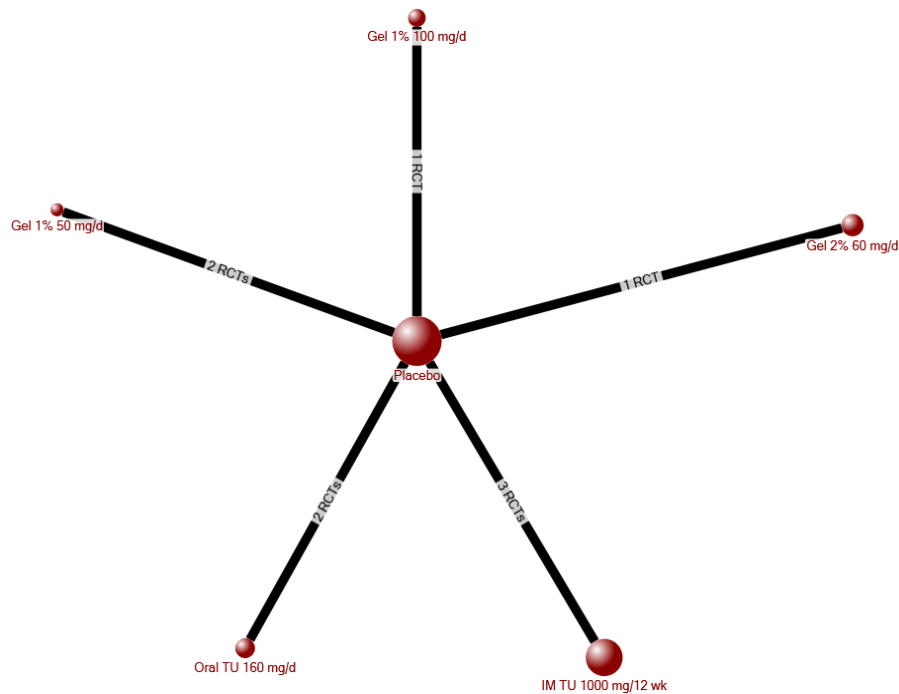
*Higher score indicates improved function for all scales used to evaluate this outcome.

†Based on difference in means between placebo and TRT group after treatment.

‡Data were reported as median (range). Median was assumed to be equal to mean for data analysis.

The evidence network for erectile function included 1138 participants (Figure 3.9). A total of 5 treatments were included in the network, providing 12 comparisons based on 9 trials each with 2 arms and 1 trial with 3 arms.

FIGURE 3.9: EVIDENCE NETWORK FOR ERECTILE FUNCTION



Compared with placebo, none of the testosterone replacement therapies significantly improved erectile function (Table 3.19), and there were no differences among the treatments. Although there were significant estimates of efficacy for 1% gel (50 mg/d) and IM TU (1000 mg/12 wk) from the direct evidence, these estimates were no longer statistically significant after indirect evidence was incorporated under the random-effects model (Table 3.20, Figure 3.10).

TABLE 3.19: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES

	Standardized mean difference (standard deviation)*					
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/12 wk
Gel 1%, 50 mg/d	0.54 (0.55)	—				
Gel 1%, 100 mg/d	0.23 (0.73)	−0.30 (0.91)	—			
Gel 2%, 60 mg/d	0.08 (0.73)	−0.45 (0.91)	−0.15 (1.04)	—		
Oral TU, 160 mg/d	0.38 (0.43)	−0.15 (0.70)	0.15 (0.85)	0.30 (0.85)	—	
IM TU, 1000 mg/12 wk	0.31 (0.36)	−0.22 (0.66)	0.08 (0.82)	0.24 (0.82)	−0.06 (0.52)	—
Note: IM = intramuscular injection, TU = testosterone undecanoate. *Random-effects model.						

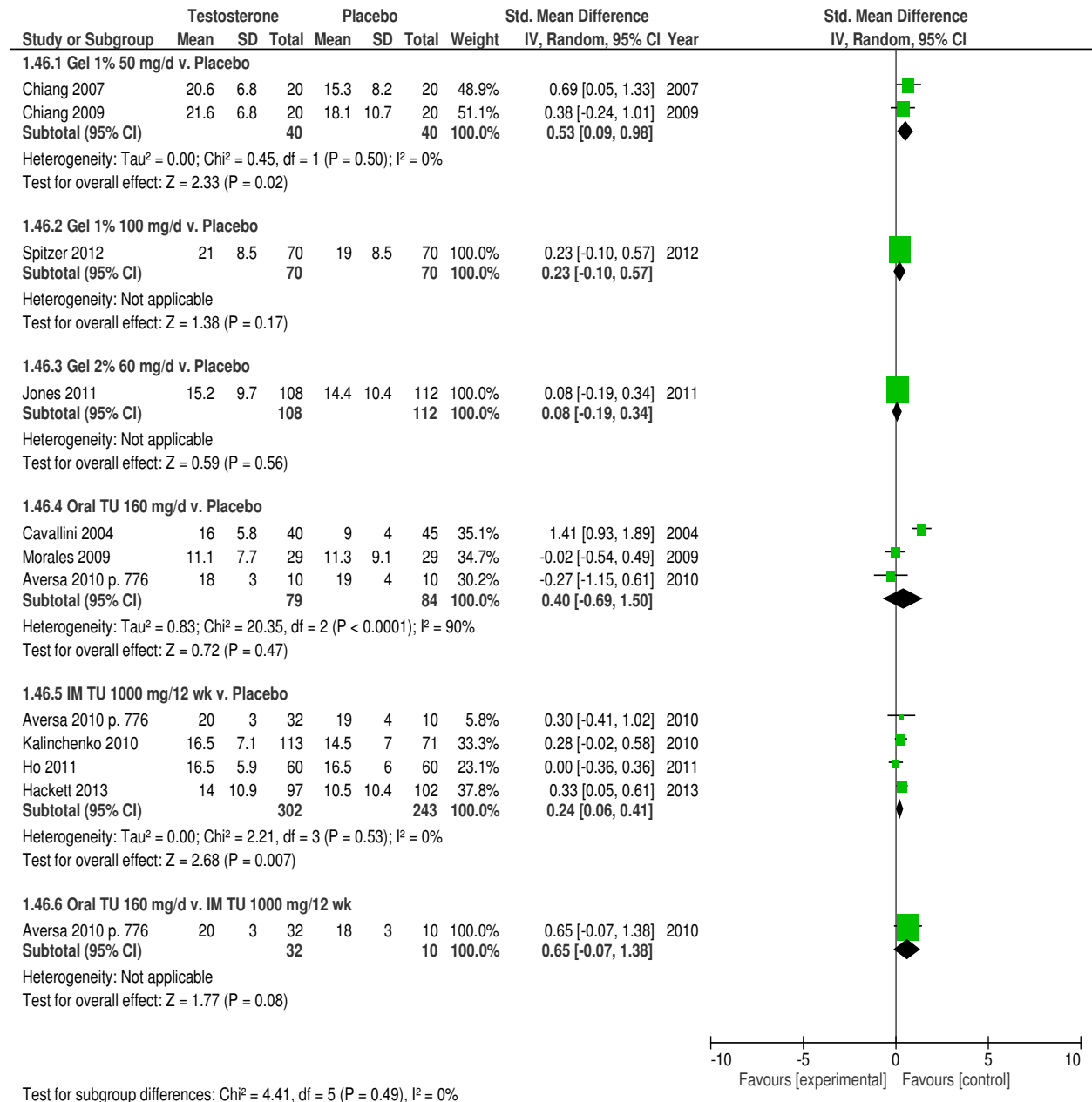
TABLE 3.20: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR ERECTILE FUNCTION

Comparison		Direct evidence			Direct + indirect evidence (derived from NMA); SMD (95% CrI)	
		SMD (95% CI)	No. of studies	I^2 , %	Random-effects model	Fixed-effects model
Gel 1% 50 mg/d	Placebo	0.53* (0.09 to 0.98)	2	0	0.53 (−0.57 to 1.63)	0.53* (0.09 to 0.98)
Gel 1% 100 mg/d	Placebo	0.23 (−0.10 to 0.57)	1	NA	0.23 (−1.25 to 1.70)	0.23 (−0.10 to 0.56)
Gel 2% 60 mg/d	Placebo	0.08 (−0.19 to 0.34)	1	NA	0.08 (−1.38 to 1.54)	0.08 (−0.18 to 0.34)
Oral TU 160 mg/d	Placebo	0.40 (−0.69 to 1.50)	3	90	0.38 (−0.51 to 1.22)	0.54* (0.23 to 0.85)
IM TU 1000 mg/12 wk	Placebo	0.24* (0.06 to 0.41)	4	0	0.31 (−0.41 to 1.04)	0.27* (0.23 to 0.85)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.65 (−0.07 to 1.38)	1	NA	−0.06 (−1.06 to 1.01)	−0.27 (−0.61 to 0.07)
DIC					9.20	23.34
Total residual deviance					11.47 (10 points)	30.88 (10 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criterion, IM = intramuscular injection, SMD = standardized mean difference, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

* $p < 0.05$.

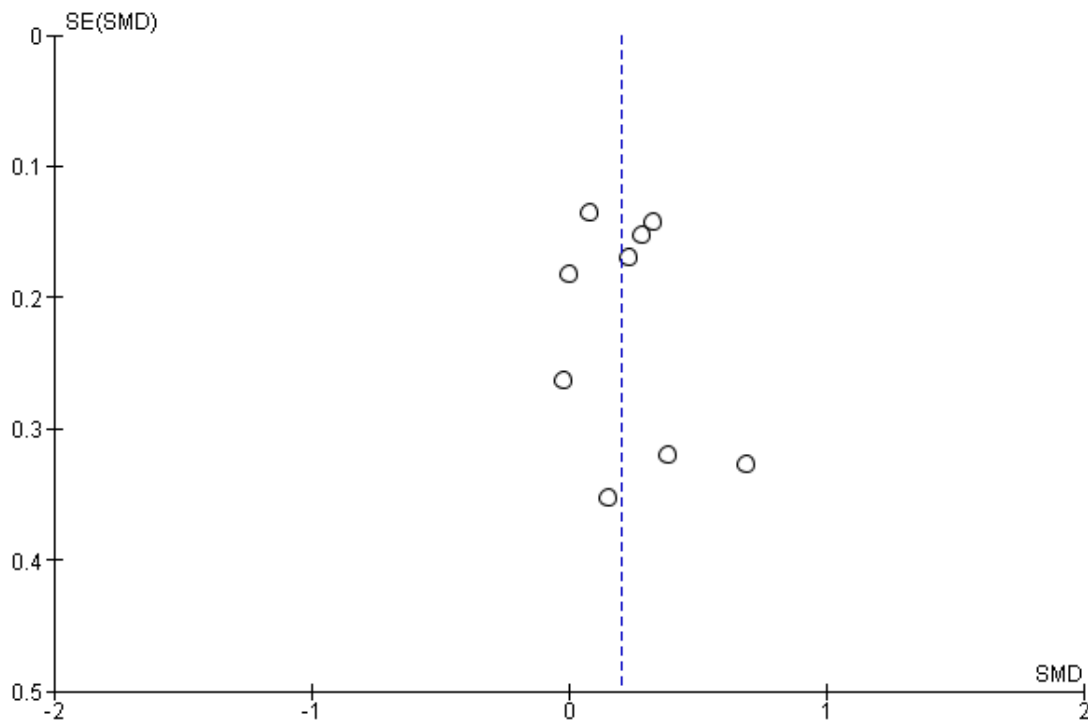
FIGURE 3.10: DIRECT EVIDENCE FOR ERECTILE FUNCTION



PUBLICATION BIAS

Publication bias was evaluated among the 9 trials that assessed erectile function using a 2-arm parallel design. The funnel plot for erectile function shows a clustering of trials to the left of zero SMD, regardless of standard error (Figure 3.11). There were no trials with a negative SMD. This may suggest potential publication bias, because there were no trials that reported a negative effect of testosterone on erectile function. This data should be interpreted with caution, however, because the analysis was based on 9 trials, while at least 10 are generally thought to be required for proper assessment of publication bias (11).

FIGURE 3.11: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — ERECTILE FUNCTION



SENSITIVITY ANALYSES

INFLUENCE OF FUNDING

Four trials reported having no industry funding (14, 28, 41, 49) (Table 3.18). The evidence network for erectile function based on trials with no industry funding involved 323 participants and 3 treatments. Four comparisons were made, based on 4 trials each with 2 arms. There were no significant differences in erectile function between the testosterone treatments and placebo or among the treatments when only trials with no industry funding were considered (Table 3.21).

TABLE 3.21: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS WITH THAT REPORTED HAVING NO INDUSTRY FUNDING

	Standardized mean difference (standard deviation)*			
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral, TU 160 mg/d
Gel 1%, 50 mg/d	0.37 (2.59)	—		
Gel 1%, 100 mg/d	0.23 (2.58)	−0.15 (3.66)	—	
Oral TU, 160 mg/d	0.70 (1.84)	0.33 (3.18)	0.47 (3.18)	—
Note: TU = testosterone undecanoate. *Random-effects model.				

RISK OF BIAS

Five trials were assessed as being at low risk of bias (28, 29, 34, 37, 41) (Table 3.22). Three treatments were compared in these trials, involving a total of 701 participants. The network comprised 5 comparisons, based on 5 trials each with 2 arms.

Compared with placebo, there were no significant differences in erectile function for any testosterone replacement therapy (Table 3.23). There were no significant differences between the treatments.

TABLE 3.22: RISK OF BIAS ASSESSMENT OF TRIALS THAT ASSESSED ERECTILE FUNCTION

Trial	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Hackett 2013	Low	Low	Low	Low
Spitzer 2012	Low	Low	Low	Low
Ho 2011	Low	Low	Low	Low
Jones 2011	Unclear	Low	High	High
Aversa 2010, p.776	Unclear	Low	Unclear	Unclear
Kalinchenko 2010	Low	Low	Low	Low
Morales 2009	Low	Low	Low	Low
Chiang 2009	Unclear	Low	High	High
Chiang 2007	Unclear	Unclear	High	High
Cavallini 2004	Unclear	Unclear	Unclear	Unclear

TABLE 3.23: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS

	Standardized mean difference (standard deviation)*			
	Placebo	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU 1000 mg/12 wk
Gel 1%, 100 mg/d	0.24 (0.93)	—		
Oral TU, 160 mg/d	−0.02 (0.94)	−0.26 (1.34)	—	
IM TU 1000 mg/12 wk	0.21 (0.53)	−0.03 (1.07)	0.23 (1.09)	—

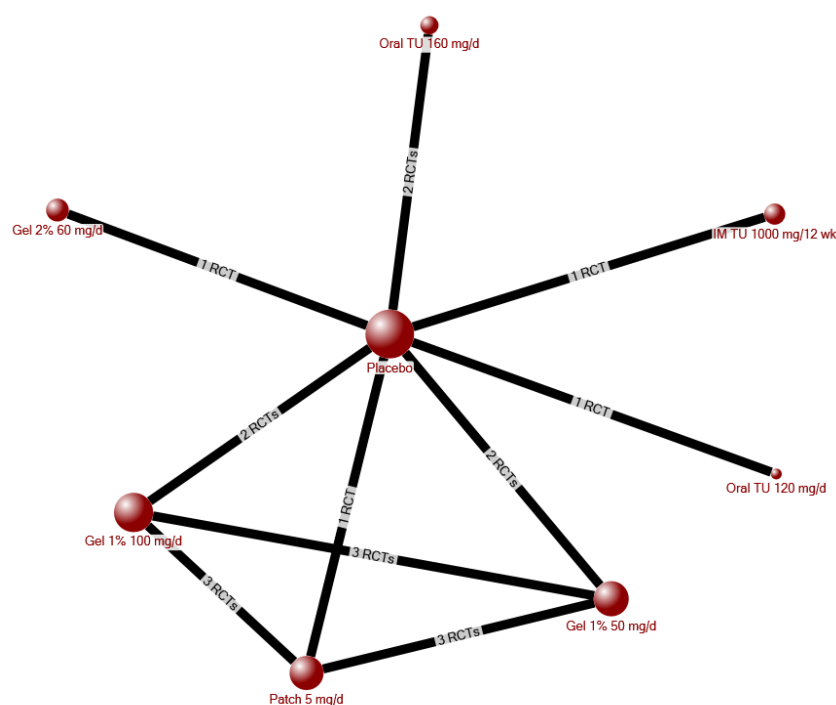
Note: TU = testosterone undecanoate.
*Random-effects model.

LIBIDO

Ten trials assessed the effect of testosterone supplementation on libido; all were included in the network meta-analysis (14, 28, 34, 36, 41, 48, 50, 52-54). The treatment duration was between 12 weeks and 1 year (Table 3.24). The most common scale used to assess libido was the IIEF scale (sexual function domain). A higher score indicated improved libido for all scales used.

The evidence network for libido included 1631 participants (Figure 3.12). A total of 7 treatments were included in the network, providing 19 comparisons based on 7 trials with 2 arms, 2 trials with 3 arms, and 1 trial with 4 arms. The consistency of the network was evaluated by plotting the posterior mean deviance of the individual data points in the inconsistency model versus those from the consistency model (Appendix 6). There was no evidence of inconsistency in the network.

FIGURE 3.12: EVIDENCE NETWORK FOR LIBIDO



Compared with placebo, there were no significant differences in libido for any testosterone replacement therapy, and there were no differences among the treatments in the head-to-head comparisons (Table 3.25). However, there were discrepancies between evidence from the primary trials and from the network meta-analysis. In the primary trials, significant positive effects were reported for intramuscular injection of testosterone undecanoate (1000 mg/12 wk) and testosterone 1% gel (100 mg/d); these estimates were not statistically significant in the random-effects model after the indirect evidence was incorporated (Table 3.26, Figure 3.13).

TABLE 3.24: CHARACTERISTICS OF TRIALS THAT ASSESSED LIBIDO

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study*	Industry funding	Comment
							Before	After			
Hackett 2013	T2DM and symptoms of hypogonadism	IIEF, SD domain	Higher score indicates improved libido	30	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	5.29 (2.22) 5.19 (2.03)	4.96 (4.44) 5.69 (2.34)	No†	Yes	16% were taking a PDE5 inhibitor; more men in the placebo group 18% v. 8% in the active group were taking a PDE5 inhibitor; 85% had at least mild ED
Spitzer 2012	Erectile dysfunction	MSHQ, SD domain	Higher score indicates improved libido	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	10.0 (3.2) 9.8 (3.2)	10.0 (3.2) 10.5 (4.3)	No	No	Participants in both groups were taking sildenafil on demand
Jones 2011	MetS or T2D with at least 2 symptoms of hypogonadism	IIEF, SD domain	Higher score indicates improved libido	52	Placebo (112) Gel 2%, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	5.6 (2.47) 5.3 (2.13)	5.8 (2.55) 6.3 (2.21)	No	Yes	
Chiang 2009	Hypogonadal men	IIEF, SD domain	Higher score indicates improved libido	12	Placebo (20) Gel 1%, 50 mg/d (20)	NR	6.3 (2.4) 5.0 (1.6)	6.3 (2.4) 6.4 (1.6)	No	NR	Eligible age range was 20–75 yr
Morales 2009	Sexual dysfunction	IIEF, SD domain	Higher score indicates improved libido	16	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59 (10.6)	5.1 (2.0) 4.9 (1.5)	6.1 (2.1) 5.0 (2.0)	No	Yes	Significant change in placebo group from baseline
Cavallini 2004	Symptoms of androgen decline	IIEF, SD domain	Higher score indicates improved libido	26	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	3 (0.5) ⁺ 4 (0.75) ⁺	3 (0.5) ⁺ 7 (0.75) ⁺	Yes	No	
Boyanov 2003	T2DM, obesity, and “symptoms of andropause or erectile dysfunction”	Subscale of PADAM questionnaire	Higher score indicates improved libido	12	No treatment (24) Oral TU, 120 mg/d (24)	57.5 (4.8) (not reported by group)	1.50 (1.0) 1.25 (1.0)	1.68 (1.25) 2.13 (0.61)	No	NR	
McNicholas 2003	≥ 1 symptom of “low T	PDQ	Higher score indicates improved libido	12	Gel 1%, 50 mg/d (68) Gel 1%, 100 mg/d (68) Patch, 5 mg/d (72)	59.0 (9.5) 56.7 (10.3) 57.9 (10.2)	1.6 (1.1) 1.9 (1.4) 1.8 (1.2)	2.4 (1.1) 2.6 (1.4) 2.3 (1.2)	• Gel 50 v. patch: No • Gel 100 v. patch: No • Gel 50 v. gel 100: No	Yes	Double blind for gels; open-label for patch
Steidle 2003	≥ 1 symptom of “low T	PDQ	Higher score indicates improved libido	12	Placebo (99) Patch, 5 mg/d (102) Gel 1%, 50 mg/d (99) Gel 1%, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	2.1 (1.4) 2.2 (1.4) 2.3 (1.4) 2.4 (1.4)	2.6 (1.4) 2.8 (1.4) 2.8 (1.4) 3.4 (1.4)	• Patch v. placebo: No • Gel 50 v. placebo: No • Gel 100 v.	Yes	

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study*	Industry funding	Comment
							Before	After			
Wang 2000	Primary, secondary or late-onset hypogonadism	7 point Likert scale	Higher score indicates improved libido	12	Patch 5 mg/d (76)	51.1 (NR)	2.0 (4.4)	2.7 (4.4)	placebo: Yes • Gel 50 v. patch: No • Gel 100 v. patch: No • Gel 50 v. gel 100: No	Mix	Double blind for gels; open-label for patch
					Gel 1%, 50 mg/d (73)	51.3 (NR)	2.1 (4.3)	3.2 (4.3)			
					Gel 1%, 100 mg/d (78)	51.0 (NR)	1.9 (4.4)	3.6 (4.4)			

Note: IIEF = International Index of Erectile Function, MSHQ = Male Sexual Health Questionnaire, PADAM = Partial Androgen Deficiency in Aging Men, PDQ = Psychosexual Daily Questionnaire, SD = sexual dysfunction, T2DM = type 2 diabetes mellitus, TU = testosterone undecanoate.

*Based on difference in means between placebo and TRT group after treatment.

†Data were reported as median (range). Median was assumed to be equal to mean for data analysis.

‡Authors report significance after adjustment but rationale for adjustment not provided.

TABLE 3.25: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES

Treatment	Standardized mean difference (standard deviation)*							
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Oral TU, 120 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/12 wk
Patch, 5 mg/d	0.04 (1.33)	—						
Gel 1%, 50 mg/d	0.10 (1.18)	0.06 (1.10)	—					
Gel 1%, 100 mg/d	0.29 (1.18)	0.25 (1.11)	0.19 (1.05)	—				
Gel 2%, 60 mg/d	0.21 (1.95)	0.17 (2.35)	0.11 (2.27)	−0.08 (2.28)	—			
Oral TU, 120 mg/d	0.45 (1.97)	0.41 (2.38)	0.35 (2.30)	0.16 (2.30)	0.24 (2.77)	—		
Oral TU, 160 mg/d	2.21 (1.40)	2.26 (1.94)	2.21 (1.83)	2.01 (1.84)	2.10 (2.42)	1.85 (2.43)	—	
IM TU, 1000 mg/12 wk	0.30 (1.96)	0.26 (2.38)	0.20 (2.29)	−0.01 (2.29)	0.09 (2.77)	−0.15 (2.43)	−2.01 (2.41)	—

IM = intramuscular injection, TU = testosterone undecanoate.
 *Random-effects model

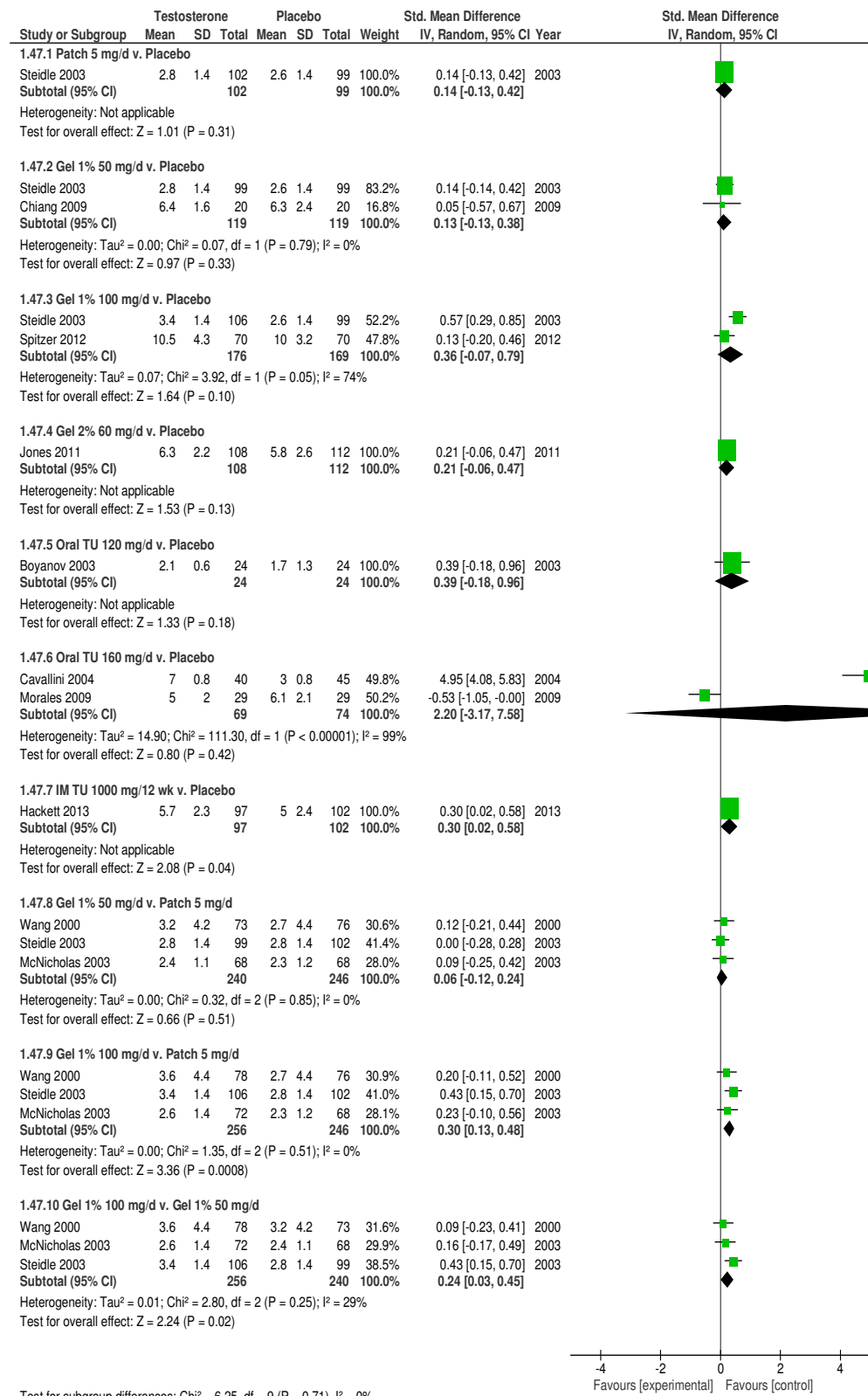
TABLE 3.26: COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR THE EFFECT OF TESTOSTERONE REPLACEMENT THERAPIES ON LIBIDO

Comparison		Direct evidence			Direct + indirect evidence (derived from NMA), SMD (95% CI)	
		SMD (95% CI)	No. of studies	I ² , %	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	0.14 (−0.13 to 0.42)	1	NA	0.04 (−2.66 to 2.75)	0.0 (−0.15 to 0.28)
Gel 1% 50 mg/d	Placebo	0.13 (−0.13 to 0.38)	2	0	0.10 (−2.27 to 2.50)	0.12 (−0.09 to 0.34)
Gel 1% 100 mg/d	Placebo	0.36 (−0.07 to 0.79)	2	74	0.29 (−2.09 to 2.68)	0.34* (0.15 to 0.53)
Gel 2% 60 mg/d	Placebo	0.21 (−0.06 to 0.47)	1	NA	0.21 (−3.72 to 4.15)	0.21 (−0.05 to 0.47)
Oral TU 120 mg/d	Placebo	0.39 (−0.18 to 0.96)	1	NA	0.45 (−3.51 to 4.45)	0.45 (−0.12 to 1.02)
Oral TU 160 mg/d	Placebo	2.20 (−3.17 to 7.58)	2	99	2.21 (−0.48 to 5.16)	0.94* (0.49 to 1.39)
IM TU 1000 mg/12 wk	Placebo	0.30* (0.02 to 0.58)	1	NA	0.30 (−3.67 to 4.29)	0.30* (0.02 to 0.58)
Gel 1% 50 mg/d	Patch 5 mg/d	0.06 (−0.12 to 0.24)	3	0	0.06 (−2.16 to 2.28)	0.06 (−0.12 to 0.23)
Gel 1% 100 mg/d	Patch 5 mg/d	0.30* (0.13 to 0.48)	3	0	0.25 (−1.98 to 2.47)	0.27* (0.10 to 0.44)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	0.24* (0.03 to 0.45)	3	29	0.19 (−1.92 to 2.29)	0.21* (0.04 to 0.39)
DIC					6.35	117.06
Total residual deviance					14.34 (10 points)	132.10 (10 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criterion, IM = intramuscular injection, SMD = standardized mean difference, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

**p* < 0.05.

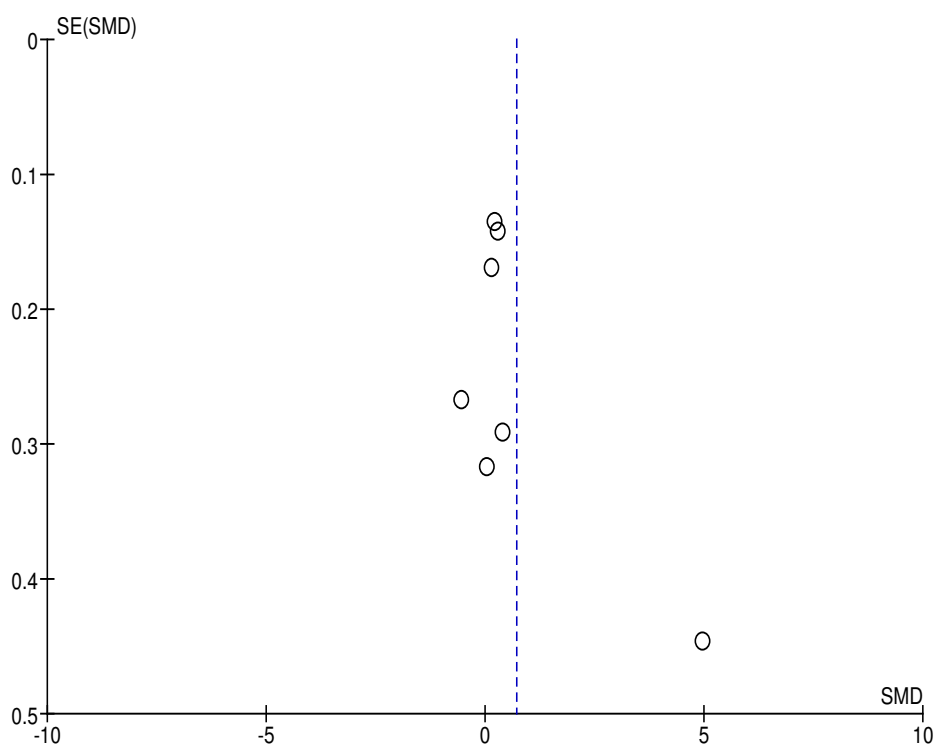
FIGURE 3.13: DIRECT EVIDENCE FOR LIBIDO



PUBLICATION BIAS

Publication bias was evaluated for the 7 trials that used a 2-arm parallel design (Figure 3.14). The SMDs of all but 1 trial were close to zero. One trial with a relatively large SE had a positive SMD, indicating a positive effect of testosterone replacement therapy on libido. There were no corresponding trials showing a negative effect, suggesting the possibility of publication bias. However, this analysis was based only on 7 trials, and the findings should be interpreted with caution.

FIGURE 3.14: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — LIBIDO



SENSITIVITY ANALYSES

INFLUENCE OF FUNDING

Of the 10 trials included for libido, only 2 reported no industry funding (14, 28). Spitzer and colleagues (28) reported no significant effect of 1% testosterone gel (100 mg/d; n = 70) compared with placebo (n = 70) on libido. Participants in both treatment arms of this trial were taking sildenafil on demand. Although Cavallini and colleagues (14) reported no industry funding, the authors hold a patent on one of the treatments being investigated in their trial (L-carnitine; treatment arm not included in our analyses). The authors reported a significant effect of oral testosterone undecanoate (160 mg/d; n = 40) compared with placebo (n = 45) on libido.

The network meta-analysis of trials that reported no industry funding involved 2 treatments and 225 participants. Both trials included in the network were involved 2 arms. Compared with placebo, neither treatment had a significant effect on libido. Similarly, there was no significant difference in libido between the 2 treatments (Table 3.27).

TABLE 3.27: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS WITH THAT REPORTED HAVING NO INDUSTRY FUNDING

	Standardized mean difference (standard deviation)*		
	Placebo	Gel 1%, 100 mg/d	Oral TU, 160 mg/d
Gel 1%, 100 mg/d	0.12 (2.88)	—	
Oral TU, 160 mg/d	5.27 (2.91)	5.14 (4.11)	—
Note: TU = testosterone undecanoate *Random-effects model			

RISK OF BIAS

Three trials were assessed as being at overall low risk of bias (28, 34, 41) (Table 3.28). The network comprised 3 comparisons based on 3 trials, each with 2 arms, and involved 397 participants.

TABLE 3.28: RISK OF BIAS ASSESSMENT OF TRIALS THAT ASSESSED LIBIDO

Trials	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Hackett 2013	Low	Low	Low	Low
Spitzer 2012	Low	Low	Low	Low
Jones 2011	Unclear	Low	High	High
Morales 2009	Low	Low	Low	Low
Chiang 2009	Unclear	Low	High	High
Boyanov 2003	Unclear	High	Low	High
Cavallini 2004	Unclear	Unclear	Unclear	Unclear
McNicholas 2003	Unclear	High	High	High
Wang 2000	Unclear	High	High	High
Steidle 2003	Unclear	High	High	High

Compared with placebo, there were no significant differences in libido for any of the testosterone replacement therapies included in this network (Table 3.29). There were no significant differences among the treatments in the head-to-head comparison.

TABLE 3.29: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES AMONG TRIALS AT LOW RISK OF BIAS

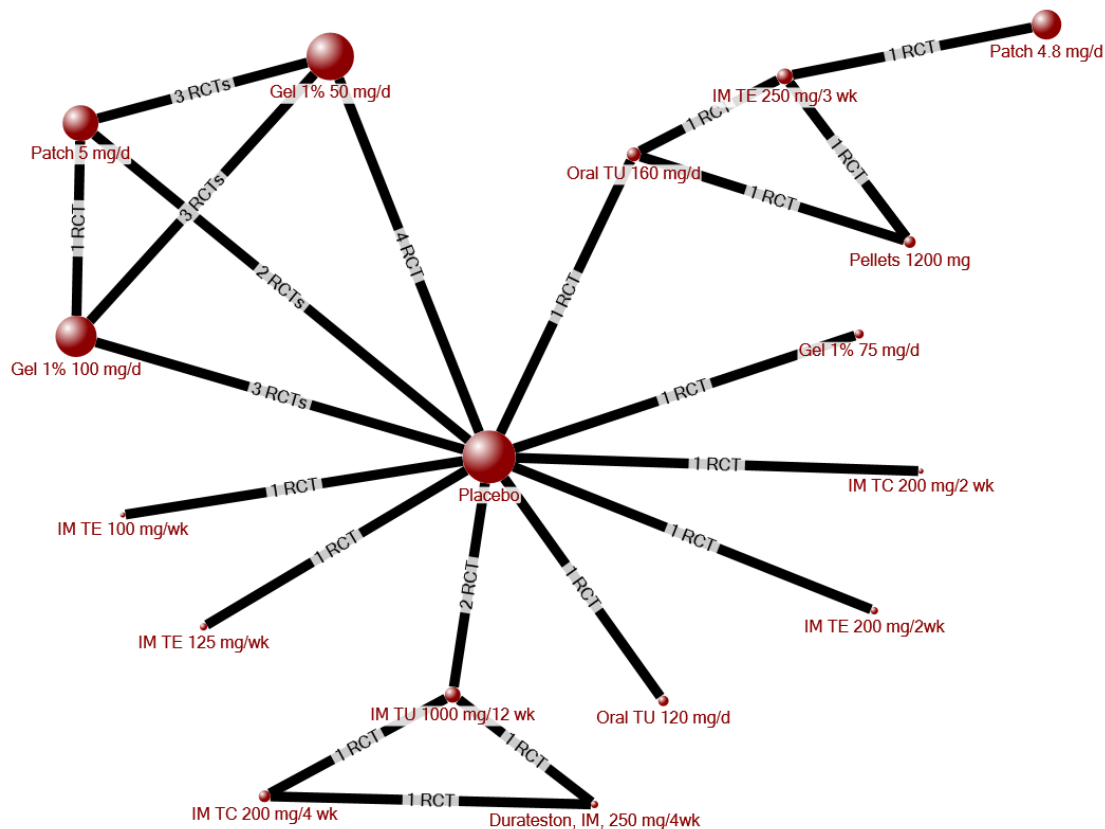
	Standardized mean difference (standard deviation)*			
	Placebo	Gel 1%, 100 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/12 wk
Gel 1%, 100 mg/d	0.13 (2.90)	—		
Oral TU, 160 mg/d	−0.53 (2.90)	−0.66 (4.12)	—	
IM TU, 1000 mg/12 wk	0.31 (2.91)	0.18 (4.12)	0.84 (4.13)	—
Note: IM = intramuscular injection, TU = testosterone undecanoate *Random-effects model				

TESTOSTERONE LEVELS

3 MONTHS

A total of 25 trials reported serum total testosterone levels after 3 months of treatment (14, 21, 22, 24, 28, 32, 35, 43, 44, 46, 48-50, 52-63). Of these, 23 provided data suitable for analysis. One trial was excluded because it reported only mean change from baseline (35), and 1 was excluded because it reported achievement of a normal testosterone level as a dichotomous outcome (43). The evidence network for total testosterone level at 3 months included 23 trials with a total of 2180 participants (Figure 3.15). Overall, 15 treatments were compared, providing 36 comparisons based on 18 trials with 2 arms, 4 trials with 3 arms, and 1 trial with 4 arms. There was no evidence of inconsistency in the model (Appendix 6).

FIGURE 3.15: EVIDENCE NETWORK DIAGRAM FOR TOTAL TESTOSTERONE LEVEL AFTER 3 MONTHS OF TREATMENT



After 3 months of treatment, 6 of 15 treatments resulted in a significant increase in serum total testosterone compared to placebo (Table 3.30). Of these, testosterone pellets were associated with the highest increase. In the head-to-head comparisons, testosterone pellets were significantly better at 3 months than testosterone patch (4.8 mg/d, 5 mg/d), gel 1% (50 mg/d), oral testosterone undecanoate (120 mg/d, 160 mg/d), intramuscular testosterone undecanoate (1000 mg/12 wk), intramuscular testosterone enanthate (200 mg/2 wk, 250 mg/3 wk), intramuscular testosterone cypionate (200 mg/4 wk), and Durateston (250 mg/4 wk) (Table 3.31).

TABLE 3.30: TOTAL TESTOSTERONE LEVEL, 3 MONTHS — MEAN DIFFERENCE (STANDARD DEVIATION)

	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 12 wk	IM TE 100 mg/ wk	IM TE 125 mg/ wk	IM TE 200 mg/ 2 wk	IM TE 250 g/ 3wk	IM TC 200 mg/ 4 wk	Durateston 250 mg/4 wk
Patch 4.8 mg/d	10.12 (5.80)	—														
Patch 5 mg/d	2.53 (1.83)	-7.59 (6.07)	—													
Gel 1% 50 mg/d	5.32* (1.57)	-4.79 (6.01)	2.80 (1.79)	—												
Gel 1% 75 mg/d	7.52 (4.19)	-2.59 (7.14)	5.00 (4.57)	2.20 (4.48)	—											
Gel 1% 100 mg/d	9.61* (1.69)	-0.51 (6.04)	7.08* (1.81)	4.29* (1.74)	2.09 (4.51)	—										
Oral TU 120 mg/d	4.35 (3.46)	-5.77 (6.78)	1.82 (3.90)	-0.98 (3.79)	-3.18 (5.44)	-5.26 (3.84)	—									
Oral TU 160 mg/d	-0.03 (3.35)	-10.15 (4.76)	-2.56 (3.79)	-5.35 (3.69)	-7.55 (5.36)	-9.64* (3.73)	-4.38 (4.83)	—								
Pellets 1200 mg	19.60* (5.15)	9.48* (4.67)	17.07* (5.46)	14.28* (5.38)	12.08 (6.63)	9.99 (5.42)	15.25* (6.23)	19.63* (3.93)	—							
IM TU 1000 mg/ 12 wk	8.13* (2.31)	-1.99 (6.27)	5.60 (2.95)	2.81 (2.80)	0.61 (4.79)	-1.48 (2.87)	3.78 (4.15)	8.16* (4.09)	-11.47* (5.67)	—						
IM TE 100 mg/wk	8.67* (3.66)	-1.45 (6.87)	6.14 (4.09)	3.34 (3.98)	1.15 (5.57)	-0.94 (4.03)	4.32 (5.01)	8.70 (4.94)	-10.93 (6.33)	0.54 (4.33)	—					
IM TE 125 mg/wk	6.79 (5.25)	-3.33 (7.83)	4.26 (5.56)	1.47 (5.48)	-0.73 (6.73)	-2.82 (5.52)	2.44 (6.28)	6.82 (6.24)	-12.81 (7.36)	-1.34 (5.73)	-1.88 (6.39)	—				
IM TE 200 mg/2 wk	6.27 (3.88)	-3.85 (6.99)	3.75 (4.29)	0.95 (4.19)	-1.25 (5.72)	-3.34 (4.25)	1.93 (5.21)	6.30 (5.14)	-13.33* (6.46)	-1.86 (4.51)	-2.40 (5.33)	-0.52 (6.49)	—			
IM TE 250 mg/3wk	10.09* (4.76)	-0.02 (3.33)	7.57 (5.08)	4.77 (5.00)	2.57 (6.33)	0.48 (5.04)	5.75 (5.90)	10.12* (3.39)	-9.51* (3.28)	1.96 (5.31)	1.43 (6.01)	3.30 (7.10)	3.82 (6.14)	—		
IM TC 200 mg/4 wk	0.51 (2.88)	-9.61 (6.48)	-2.02 (3.42)	-4.81 (3.29)	-7.01 (5.09)	-9.10* (3.34)	-3.84 (4.49)	0.54 (4.42)	-19.09* (5.90)	-7.62* (2.76)	-8.16 (4.65)	-6.28 (5.99)	-5.76 (4.83)	-9.58 (5.56)	—	
Durateston 250 mg/4 wk	1.12 (3.77)	-9.00 (6.95)	-1.41 (4.20)	-4.21 (4.09)	-6.40 (5.64)	-8.49* (4.13)	-3.23 (5.11)	1.15 (5.07)	-18.48* (6.41)	-7.01* (3.34)	-7.55 (5.25)	-5.67 (6.46)	-5.15 (5.41)	-8.97 (6.09)		—

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

* $p < 0.05$.

TABLE 3.31: TOTAL TESTOSTERONE LEVEL, 3 MONTHS — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															

1. Patch 4.8 mg/d
2. Patch 5 mg/d
3. Gel 1% 50 mg/d
4. Gel 1% 75 mg/d
5. Gel 1% 100 mg/d
6. Oral TU 120 mg/d
7. Oral TU 160 mg/d
8. Pellets 1200 mg
9. IM TU 1000 mg/12 wk
10. IM TE 100 mg/wk
11. IM TE 125 mg/wk
12. IM TE 200 mg/2 wk
13. IM TE 250 g/3wk
14. IM TC 200 mg/4 wk
15. Durateston 250 mg/4 wk

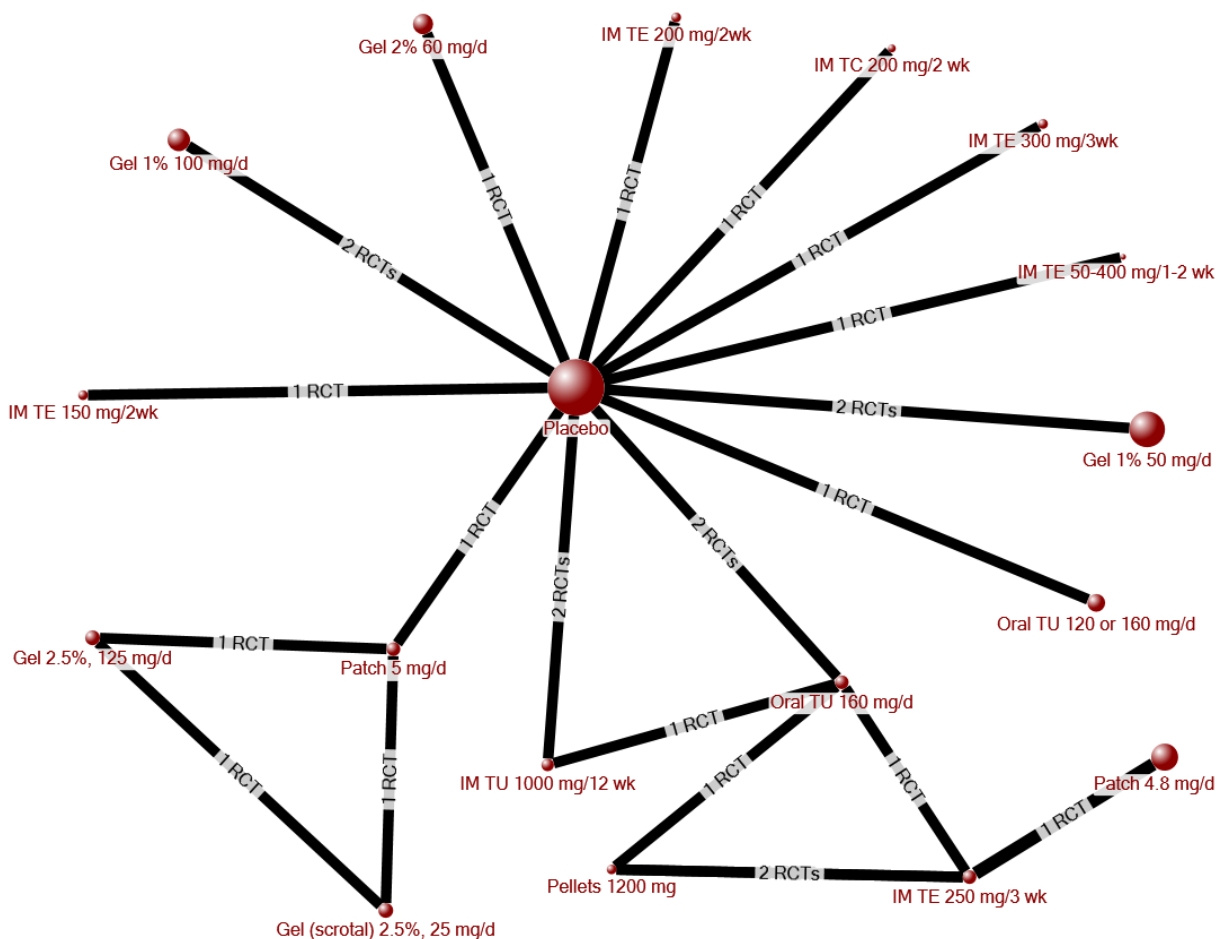
DOSE ADJUSTMENT

Of the 23 trials that reported sufficient data for analysis at 3 months, 5 allowed adjustment of the testosterone dose during the study period (21, 28, 53, 54, 56), and 18 did not report whether dose adjustment was permitted (14, 22, 24, 32, 43, 44, 46, 48-50, 52, 55, 57-62). Because dose adjustment was not well reported, we were unable to perform network meta-analysis involving only trials that did not permit dose adjustment during the treatment period.

6 MONTHS

Twenty-one trials reported serum total testosterone levels after 6 months of treatment (13, 19-21, 25, 30, 36, 40, 42, 43, 45, 47, 57, 58, 60-62, 64-67). Two trials were excluded because insufficient data for analysis were reported (45, 67): 1 because it reported only mean change from baseline (45) and 1 because it reported achievement of a normal testosterone level as a dichotomous outcome (67). The evidence network at 6 months included 19 trials with a total of 2095 participants (Figure 3.16). Overall, 17 treatments were compared, providing 25 comparisons based on 16 trials with 2 arms and 3 trials with 3 arms. There was no evidence of inconsistency in the network (Appendix 6).

FIGURE 3.16: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL AFTER 6 MONTHS OF TREATMENT



After 6 months of treatment, 8 of 17 treatments significantly increased serum total testosterone levels compared to placebo (Table 3.32). Of these, 2% testosterone gel (60 mg/d) was associated with the highest increase. Intramuscular injection of testosterone enanthate at 4 of 5 doses was also associated with high levels of serum total testosterone at 6 months. In the head-to-head comparisons, 2% testosterone gel (60 mg/d) was significantly better than 1% gel (100 mg/d), oral testosterone undecanoate (160 mg/d; T-based dose [120 or 160 mg/d]), intramuscular testosterone undecanoate (1000 mg/12 wk), and intramuscular testosterone enanthate (200 mg/2 wk) (Table 3.32). Oral testosterone undecanoate (160 mg/d) was significantly worse than testosterone patch (4.8 mg/d), 2% testosterone gel (60 mg/d), and intramuscular injection testosterone enanthate (300 mg/3 wk) (Table 3.33).

DOSE ADJUSTMENT

Of the 19 trials included in the network, only 1 reported that no dose adjustment was permitted during the treatment period (13). Eight trials reported that adjustment of the testosterone dose adjustment was permitted (19, 21, 25, 36, 40, 47, 64, 66), and 10 trials did not report whether dose adjustment was permitted (14, 20, 30, 42, 43, 57, 58, 60-62). We were unable to perform network meta-analysis involving only trials that did not permit dose adjustment during the treatment period because dose adjustment was poorly reported.

TABLE 3.32: TOTAL TESTOSTERONE LEVEL, 6 MONTHS —MEAN DIFFERENCE (STANDARD DEVIATION)

	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 100 mg/d	Gel 2% 60 mg/d	Gel 2.5% 125 mg/d	Gel 2.5% 25 mg/d (scrotal)	Oral TU 160 mg/d	Oral TU 120 or 160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 12 wk	IM TE 150 mg /2wk	IM TE 200 mg /2 wk	IM TE 250 g /3wk	IM TE 300 mg /3 wk	IM TE 50-400 mg /wk	IM TC 200 mg /2 wk
Patch 4.8 mg/d	17.38* (7.17)	—																
Patch 5 mg/d	8.48 (4.93)	-8.90 (8.75)	—															
Gel 1% 50 mg/d	8.50* (3.08)	-8.88 (7.82)	0.02 (5.82)	—														
Gel 1% 100 mg/d	6.63* (3.01)	-10.75 (7.78)	-1.84 (5.76)	-1.86 (4.30)	—													
Gel 2% 60 mg/d	18.56* (4.21)	1.19 (8.29)	10.09 (6.49)	10.07 (5.20)	11.93* (5.16)	—												
Gel 2.5% 125 mg/d	12.20 (6.46)	-5.18 (9.67)	3.72 (4.21)	3.70 (7.17)	5.57 (7.12)	-6.36 (7.72)	—											
Gel 2.5% 25 mg/d (scrotal)	7.90 (6.46)	-9.48 (9.70)	-0.58 (4.21)	-0.60 (7.17)	1.27 (7.12)	-10.66 (7.72)	-4.30 (4.21)	—										
Oral TU 160 mg/d	3.51 (2.92)	-13.87* (6.54)	-4.97 (5.73)	-4.99 (4.24)	-3.13 (4.18)	-15.06* (5.10)	-8.69 (7.09)	-4.39 (7.09)	—									
Oral TU 120 or 160 mg/d	5.66 (4.21)	-11.72 (8.34)	-2.82 (6.49)	-2.84 (5.20)	-0.97 (5.16)	-12.90* (5.96)	-6.54 (7.72)	-2.24 (7.71)	2.15 (5.11)	—								
Pellets 1200 mg	6.74 (5.23)	-10.64 (6.12)	-1.74 (7.20)	-1.76 (6.08)	0.11 (6.02)	-11.82 (6.69)	-5.46 (8.31)	-1.16 (8.33)	3.23 (4.34)	1.08 (6.71)	—							
IM TU 1000 mg/12 wk	1.53 (2.95)	-15.85* (7.43)	-6.95 (5.73)	-6.97 (4.25)	-5.10 (4.21)	-17.03* (5.11)	-10.67 (7.09)	-6.37 (7.09)	-1.98 (3.50)	-4.13 (5.13)	-5.21 (5.58)	—						
IM TE 150 mg/2wk	12.68* (4.70)	-4.70 (8.58)	4.21 (6.81)	4.19 (5.61)	6.05 (5.59)	-5.88 (6.31)	0.48 (7.97)	4.79 (7.98)	9.18 (5.54)	7.02 (6.29)	5.95 (7.05)	11.16* (5.56)	—					
IM TE 200 mg/2 wk	2.47 (4.44)	-14.91 (8.41)	-6.01 (6.62)	-6.03 (5.41)	-4.17 (5.38)	-16.09* (6.11)	-9.73 (7.82)	-5.43 (7.83)	-1.04 (5.29)	-3.19 (6.10)	-4.27 (6.83)	0.94 (5.32)	-10.22 (6.47)	—				
IM TE 250 g/3wk	12.12* (5.24)	-5.26 (4.89)	3.64 (7.22)	3.62 (6.08)	5.49 (6.04)	-6.44 (6.70)	-0.08 (8.33)	4.22 (8.35)	8.61* (4.35)	6.46 (6.71)	5.38 (3.69)	10.59 (5.60)	-0.56 (7.06)	9.65 (6.84)	—			
IM TE 300 mg/ 3wk	18.28* (4.73)	0.91 (8.59)	9.81 (6.83)	9.79 (5.66)	11.65* (5.61)	-0.28 (6.32)	6.08 (7.99)	10.39 (8.00)	14.78* (5.55)	12.62 (6.33)*	11.55 (7.01)	16.76* (5.58)	5.60 (6.70)	15.82* (6.49)	6.16 (7.04)	—		
IM TE 50-400 mg/wk	14.76 (5.92)*	-2.62 (9.28)	6.29 (7.71)	6.27 (6.68)	8.13 (6.65)	-3.80 (7.26)	2.56 (8.76)	6.87 (8.77)	11.26 (6.60)	9.10 (7.26)	8.03 (7.89)	13.24 (6.61)*	2.08 (7.56)	12.30 (7.42)	2.64 (7.88)	-3.52 (7.58)	—	
IM TC 200 mg/2 wk	6.62 (5.46)	-10.76 (9.00)	-1.86 (7.38)	-1.88 (6.26)	-0.02 (6.25)	-11.95 (6.90)	-5.58 (8.47)	-1.28 (8.47)	3.11 (6.20)	0.96 (6.88)	-0.12 (7.55)	5.09 (6.21)	-6.07 (7.19)	4.15 (7.00)	-5.50 (7.57)	-11.67 (7.23)	-8.15 (8.08)	—

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

* $p < 0.05$.

TABLE 3.33: TOTAL TESTOSTERONE LEVEL, 6 MONTHS — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	
9																	
10																	
11																	
12																	
13																	
14																	
15																	
16																	
17																	

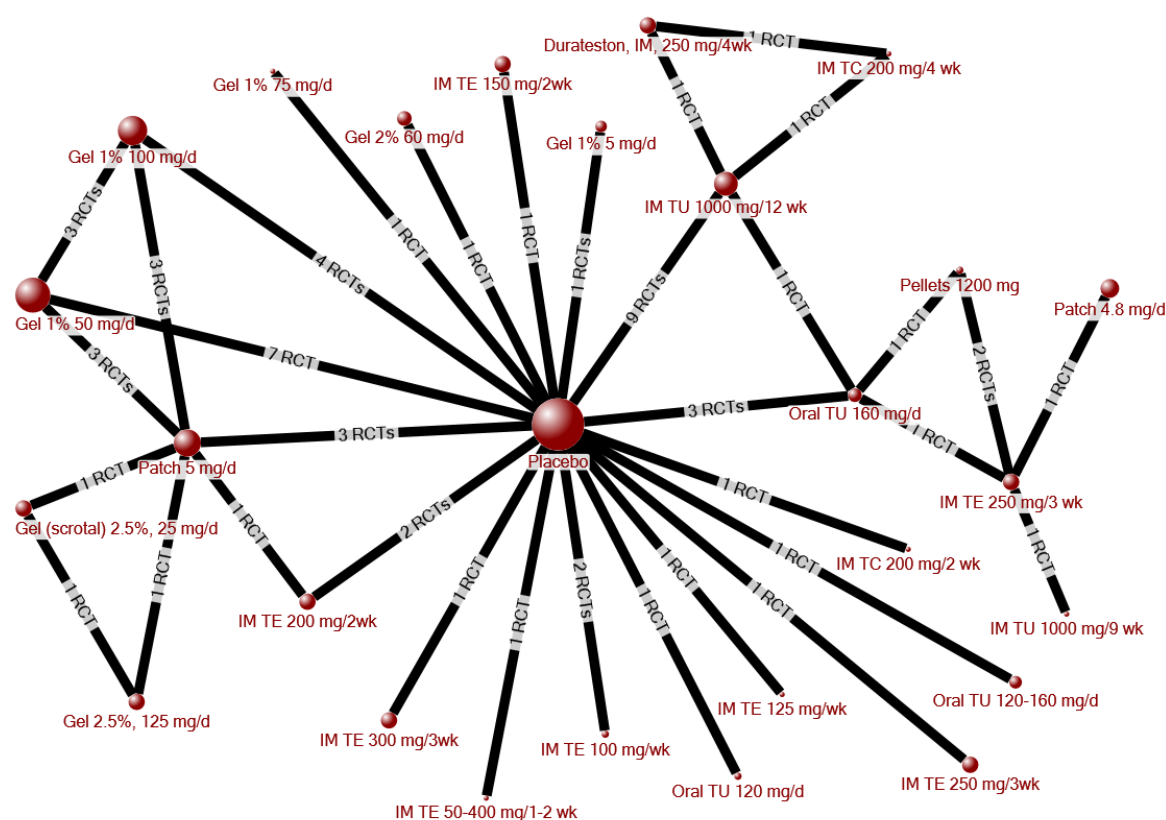
1. Patch 4.8 mg/d	8. Oral TU 160 mg/d	15. IM TE 300 mg/ 3 wk
2. Patch 5 mg/d	9. Oral TU 120-160 mg/d	16. IM TE 50-400 mg/ 1-2 wk
3. Gel 1% 50 mg/d	10. Pellets 1200 mg	17. IM TC 200 mg/ 2 wk
4. Gel 1% 100 mg/d	11. IM TU 1000 mg/ 12 wk	
5. Gel 2% 60 mg/d	12. IM TE 150 mg/ 2wk	
6. Gel 2.5% 125 mg/d	13. IM TE 200 mg/ 2 wk	
7. Gel 2.5% 25 mg/d (scrotal)	14. IM TE 250 g/ 3wk	

END OF TREATMENT

Fifty trials reported serum total testosterone levels at the end of treatment (13, 14, 19-25, 28-33, 35-38, 40-50, 52-62, 64, 66-73). Of these, 46 provided data suitable for analysis; 4 were excluded because they did not report sufficient data for analysis (1 trial reported values for the testosterone group only (73), 3 reported mean change only (35, 45, 67)). Of the trials included in the network, the treatment duration ranged from 12 weeks (9 trials) to 36 months (1 trial); all but 2 trials were between 12 weeks and 1 year duration. The evidence network for serum total testosterone at the end of study included 46 trials with a total of 4277 participants (Figure 3.17). Overall, 25 treatments were compared, providing 63 comparisons based on 39 trials with 2 arms, 6 trials with 3 arms, and 1 trial with 4 arms. Analysis of the

posterior mean deviance from the inconsistency and consistency models did not suggest inconsistency (Appendix 6).

FIGURE 3.17: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL AT END OF TREATMENT



At the end of treatment, 11 of 25 treatments significantly increased serum total testosterone compared to placebo (Table 3.34). Of these, 2% testosterone gel and intramuscular testosterone enanthate (300 mg/3 wk) were associated with the greatest increase. Of the treatments involving intramuscular testosterone enanthate, all but 1 significantly increased total testosterone (Table 3.3). In the head-to-head comparisons, 2% testosterone gel (60 mg/d) and intramuscular testosterone enanthate (300 mg/d) were significantly better than most other products (Table 3.34, Table 3.35). Although not all treatments resulted in significant differences compared with placebo, the testosterone levels in the treatment group were in the normal range (> 12 nmol/L) in most trials by the end of the treatment period (Table 3.34).

TABLE 3.34: TOTAL TESTOSTERONE LEVEL, END OF TREATMENT —MEAN DIFFERENCE (STANDARD DEVIATION)

	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 5 mg/d	Gel 1% 50 mg/d	Gel 1% 1% 75 mg/d	Gel 1% 100 mg/d	Gel 2% 60 mg/d	Gel 2.5% 125 mg/d	Gel 2.5% 25 mg/d (scrotal)	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 9 wk	IM TU 1000 mg/ 12 wk	IM TE 100 mg/wk	IM TE 125 mg/wk	IM TE 150 mg/2wk	IM TE 200 mg/ 250 g/ 3wk	IM TE 300 mg/ 3wk	IM TE 50-400 mg/ 1-2 wk	IM TC 200 mg/ 2wk	IM TC 250 mg/ 4wk	Durates ton 250 mg/4 wk
Patch 4.8 mg/d	7.98 (5.7)	—																							
Patch 5 mg/d	0.57 (1.78)	-7.41 (5.99)	—																						
Gel 1% 5 mg/d	3.77 (4.35)	-4.21 (7.17)	3.20 (4.70)	—																					
Gel 1% 50 mg/d	4.36* (1.49)	-3.62 (5.91)	3.78* (1.91)	0.59 (4.60)	—																				
Gel 1% 75 mg/d	7.49 (4.70)	-0.49 (7.42)	6.92 (4.67)	3.72 (4.94)	3.13 (5.00)	—																			
Gel 1% 100 mg/d	7.96* (1.71)	-0.02 (5.97)	7.39* (1.99)	4.19 (4.67)	3.61 (1.87)	0.48 (5.00)	—																		
Gel 2% 60 mg/d	19.76* (4.01)	11.78 (6.98)	19.19* (4.38)	15.99* (5.94)	15.40* (4.28)	12.27* (6.18)	11.80* (4.36)	—																	
Gel 2.5% 125 mg/d	4.22 (4.37)	-3.76 (7.19)	3.65 (3.99)	0.46 (6.16)	-0.13 (4.43)	-3.26 (6.41)	-3.74 (4.46)	-15.53* (5.90)	—																
Gel 2.5% 25 mg/d (scrotal)	0.05 (4.38)	-7.93 (7.19)	-0.53 (4.00)	-3.72 (6.17)	-4.31 (4.43)	-7.44 (6.43)	-7.92 (4.47)	-19.71* (5.90)	-4.18 (3.97)	—															
Oral TU 120 mg/d	4.28 (4.12)	-3.70 (7.03)	3.71 (4.48)	0.51 (6.00)	-0.08 (4.38)	-3.21 (6.26)	-3.68 (4.46)	-15.48* (5.74)	0.06 (5.99)	4.23 (5.99)	—														
Oral TU 160 mg/d	1.44 (2.07)	-6.54 (5.72)	0.87 (2.75)	-2.33 (4.82)	-2.91 (2.56)	-6.04 (5.15)	-6.52* (2.70)	-18.32* (4.53)	-2.78 (4.85)	1.40 (4.85)	-2.84 (4.60)	—													
Oral TU 120 or 160 mg/d	5.68 (3.98)	-2.30 (6.98)	5.11 (4.36)	1.91 (5.90)	1.33 (4.26)	-1.81 (6.16)	-2.28 (4.32)	-14.08* (5.64)	1.46 (5.91)	5.64 (5.92)	1.40 (5.72)	4.24 (4.50)	—												
Pellets 1200 mg	2.79 (3.74)	-5.19 (5.82)	2.22 (4.17)	-0.98 (5.75)	-1.57 (4.03)	-4.70 (6.03)	-5.17 (4.13)	-16.97* (5.50)	-1.44 (5.79)	2.74 (5.79)	-1.49 (5.56)	1.35 (3.52)	-2.89 (5.47)	—											
IM TU 1000 mg/9 wk	16.30* (5.20)	8.32 (6.46)	15.73* (5.49)	12.53 (6.79)	11.94* (5.41)	8.81 (7.01)	8.34 (5.48)	-3.46 (6.58)	12.08 (6.81)	16.25* (6.81)	12.02 (6.62)	14.86 (5.18)*	10.62 (5.57)	13.51* (5.28)	—										
IM TU 1000 mg/12 wk	8.82* (1.44)	0.84 (5.87)	8.25* (2.29)	5.05 (4.59)	4.47* (2.07)	1.34 (4.90)	0.86 (2.23)	-10.94* (4.25)	4.60 (4.60)	8.78 (4.61)	4.54 (4.37)	7.38* (2.37)	3.14 (4.24)	6.03 (3.95)	-7.48 (5.38)	—									
IM TE 100 mg/wk	9.52* (3.03)	1.54 (6.49)	8.94* (3.51)	5.75 (5.30)	5.16 (3.36)	2.03 (5.57)	1.55 (3.47)	-10.24* (5.03)	5.29 (5.34)	9.47 (5.33)	5.24 (5.12)	8.07* (3.67)	3.84 (5.02)	6.73 (4.80)	-6.78 (6.03)	0.69 (3.35)	—								
IM TE 125 mg/wk	6.61 (5.39)	-1.38 (7.85)	6.03 (5.68)	2.84 (6.92)	2.25 (5.59)	-0.88 (7.18)	-1.36 (5.66)	-13.15 (6.73)	2.38 (6.90)	6.56 (6.95)	2.33 (6.79)	5.16 (5.78)	0.92 (6.71)	3.82 (6.53)	-9.70 (7.49)	-2.22 (5.60)	-2.91 (6.17)	—							
IM TE 150 mg/2wk	12.65* (4.59)	4.67 (7.33)	12.08* (4.92)	8.88 (6.36)	8.29 (4.82)	5.16 (6.57)	4.69 (4.89)	-7.11 (6.11)	8.42 (6.34)	12.60* (6.37)	8.37 (6.16)	11.21* (5.03)	6.97 (6.10)	9.86 (5.92)	-3.65 (6.93)	3.83 (4.80)	3.13 (5.51)	6.04 (7.06)	—						

TABLE 3.35: HEAD-TO-HEAD COMPARISONS OF THE TESTOSTERONE REPLACEMENT THERAPIES AT END OF TREATMENT, TOTAL TESTOSTERONE LEVEL

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1																									
2																									
3																									
4																									
5																									
6																									
7																									
8																									
9																									
10																									
11																									
12																									
13																									
14																									
15																									
16																									
17																									
18																									
19																									
20																									
21																									
22																									
23																									
24																									
25																									

1. Patch 4.8 mg/d

2. Patch 5 mg/d

3. Gel 1% 5 mg/d

4. Gel 1% 50 mg/d

5. Gel 1% 75 mg/d

6. Gel 1% 100 mg/d

7. Gel 2% 60 mg/d

8. Gel 2.5% 125 mg/d

9. Gel 2.5% 25 mg/d
(scrotal)

10. Oral TU 120 mg/d

11. Oral TU 160 mg/d

12. Oral TU 120-160 mg/d

13. Pellets 1200 mg

14. IM TU 1000 mg/ 9 wk

15 IM TU 1000 mg/ 12 wk

16 IM TE 100 mg/ wk

17 IM TE 125 mg/ wk

18 IM TE 150 mg/ 2wk

19 IM TE 200 mg/ 2 wk

20 IM TE 250 g/ 3wk

21 IM TE 300 mg/ 3 wk

22 IM TE 50-400 mg/ 1-2 wk

23 IM TC 200 mg/ 2 wk

24 IM TC 200 mg/ 4 wk

25. Durateston 250 mg/4 wk

DOSE ADJUSTMENT

Of the 46 trials that reported testosterone levels at the end of treatment, 1 reported that no dose adjustment was permitted during the treatment period (13). Thirteen trials permitted dose adjustment during the study period (19, 21, 25, 28, 31, 36, 40, 47, 53, 54, 56, 64, 66), and 32 did not report whether dose adjustment was permitted (14, 20, 22-24, 29, 30, 32, 33, 37, 38, 41-44, 46-50, 52, 55, 57, 58, 60-62, 69-72). Because dose adjustment was not well reported, we were unable to perform network meta-analysis involving only trials that did not permit dose adjustment.

3.3.4 SUBGROUP ANALYSIS

In general, there were limited data for most subgroup analyses, and the findings should be interpreted with caution.

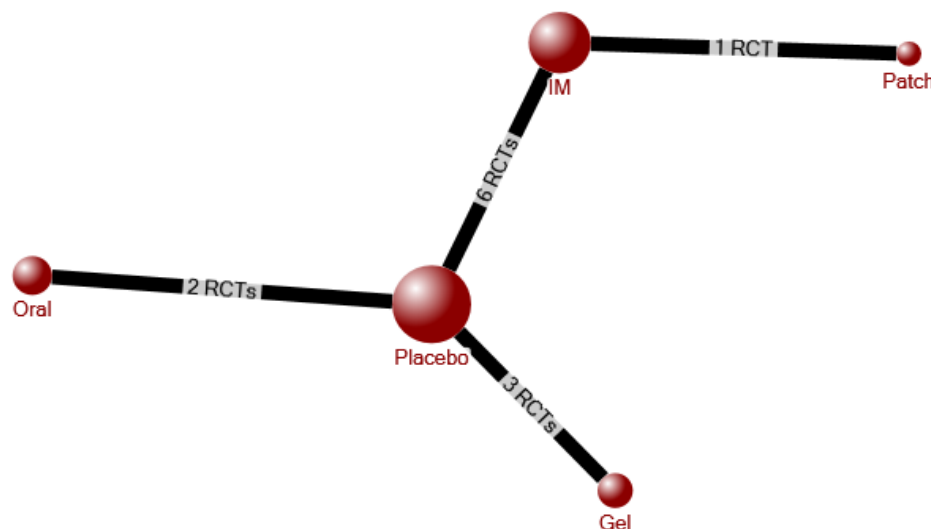
ROUTE OF ADMINISTRATION

DEPRESSION

Twelve trials reported change in depression as an outcome following testosterone replacement therapy (13, 14, 19, 24, 27-34). Of these, 2 enrolled patients with diagnosed depression at baseline. The duration of the included trials ranged from 12 weeks to 36 months.

The evidence network for the effect of testosterone replacement products on depression by route of administration included all 12 trials, involving a total of 1057 participants (Figure 3.18). Four routes of administration were compared, providing 12 comparisons based on 12 trials, each with 2 arms.

FIGURE 3.18: EVIDENCE NETWORK FOR DEPRESSION BY ROUTE OF ADMINISTRATION



Compared with placebo, oral testosterone significantly reduced the symptoms of depression (SMD -3.09 , SD 0.51), while there were no significant differences for topical or intramuscular treatments (Table 3.36). Among the treatments, oral testosterone was significantly more effective than topical or intramuscular testosterone at resolving depression (Table 3.36). However, the studies involving oral treatments were both at high overall risk of bias, and the results should be interpreted with caution.

TABLE 3.36: DEPRESSION — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION

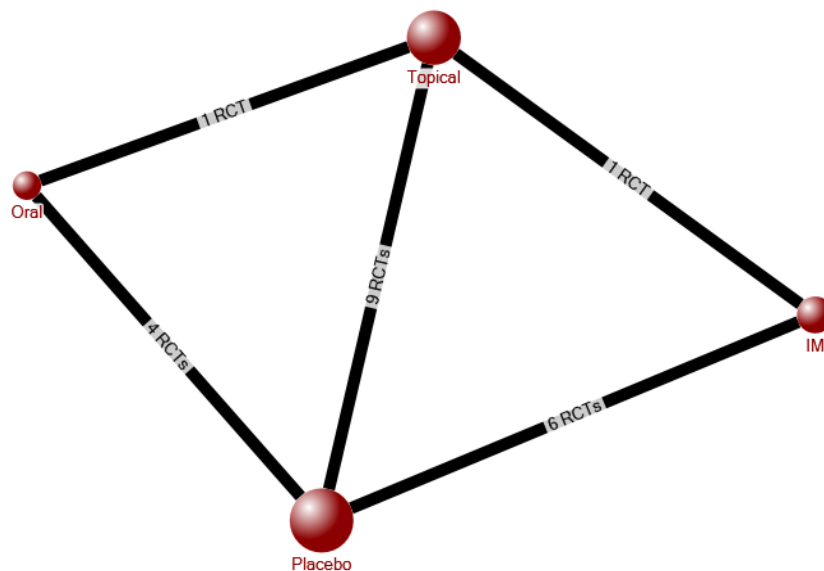
	Standardized mean difference (standard deviation)			
	Placebo	Topical	IM	Oral
Topical	-0.31 (0.38)	—		
IM	-0.24 (0.27)	0.06 (0.42)	—	
Oral	-3.09^* (0.51)	-2.78^* (0.64)	-2.85^* (0.58)	—
Note: IM = intramuscular. * $p < 0.05$.				

QUALITY OF LIFE

Twenty-one trials assessed quality of life among patients taking a testosterone replacement product (13, 21, 24, 26-29, 32, 35-45). One trial was excluded from the analysis because only mean change was reported (35). The duration of treatment was between 12 weeks and 1 year, although 7 trials (35%) involved treatment for less than 6 months.

The evidence network for the effect of testosterone replacement products on quality of life by route of administration included 19 trials, involving a total of 2578 participants (Figure 3.19). One trial was excluded from this analysis (46) because all 3 treatment arms involved intramuscular injection of a testosterone product. In the network, 4 routes of administration were compared, providing 21 comparisons based on 18 trials with 2 arms and 1 trial with 3 arms. Topical testosterone products were most frequently compared, with relatively fewer participants receiving oral or intramuscular forms (Figure 3.19). There was no evidence of inconsistency in this network (Appendix 6).

FIGURE 3.19: EVIDENCE NETWORK FOR QUALITY OF LIFE, BY ROUTE OF ADMINISTRATION



There were no significant differences between any route of administration and placebo, and there were no significant differences among the routes (Table 3.37).

TABLE 3.37: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION

	Standardized mean difference (standard deviation)			
	Placebo	Topical	IM	Oral
Topical	−0.60 (0.41)	—		
IM	−0.09 (0.48)	0.52 (0.59)	—	
Oral	−0.16 (0.62)	0.44 (0.74)	−0.07 (0.75)	—
Note: IM = intramuscular.				

ERECTILE FUNCTION

Fourteen trials reported erectile function as an outcome (14, 26, 28, 29, 35-37, 41, 45, 47-51). Four trials were excluded from the network meta-analysis: 1 reported dichotomous outcomes based on response to the International Index of Erectile Function (IIEF) scale (35), 1 reported a dichotomous outcome of “ever” v. “never” for difficulty in achieving an erection (45), 1 assessed nocturnal erectile activity (50), and 1 assessed the frequency of nocturnal erections (51). The treatment duration of the included trials ranged from 12 weeks to 1 year.

The evidence network for the effect of testosterone replacement products on erectile function by route of administration included 10 trials, involving a total of 1138 participants (Figure 3.20). In the network, 4 routes of administration were compared, providing 12 comparisons based on 9 trials with 2 arms and 1 trial with 3 arms. In this analysis, more participants were enrolled in intramuscular injection and topical treatment arms than in oral treatment arms. There was no evidence of inconsistency in this network (Appendix 6).

There were no significant differences between any route of administration and placebo, and there were no significant differences among the routes (Table 3.38).

FIGURE 3.20: EVIDENCE NETWORK FOR ERECTILE FUNCTION, BY ROUTE OF ADMINISTRATION

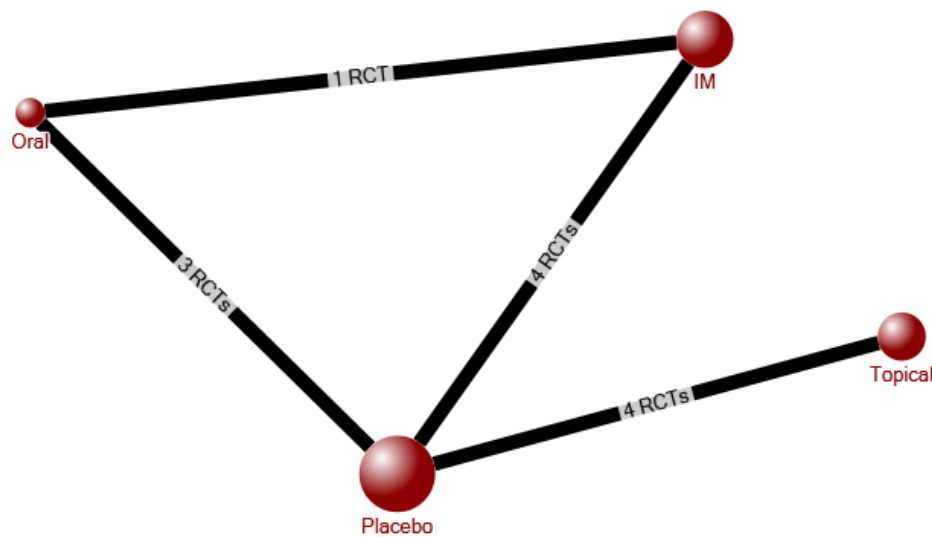


TABLE 3.38: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE THERAPIES PRODUCTS, BY ROUTE OF ADMINISTRATION

	Standardized mean difference (standard deviation)			
	Placebo	Topical	IM	Oral
Topical	0.31 (0.30)	—		
IM	0.31 (0.28)	0.00 (0.41)	—	
Oral	0.40 (0.35)	0.08 (0.46)	0.09 (0.41)	
Note: IM = intramuscular.				

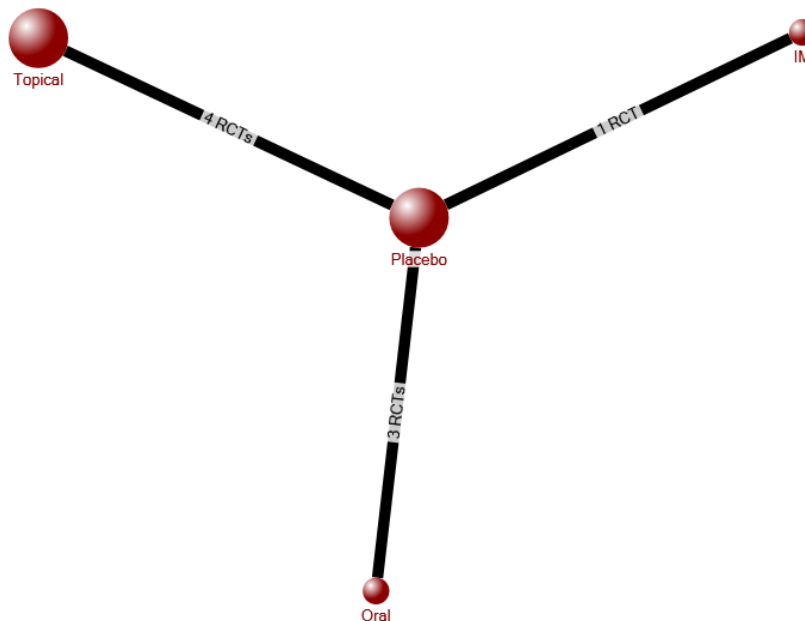
LIBIDO

Ten trials assessed the effect of testosterone supplementation on libido (14, 28, 34, 36, 41, 48, 50, 52-54). Two trials were excluded from the network analysis of the route of administration because all arms involved a topical treatment in each study (52, 53). The treatment duration among the included trials was between 12 weeks and 1 year.

The evidence network for libido included 1196 participants (Figure 3.21). Three routes of administration were compared in the network, providing 8 comparisons based on 8 trials

each with 2 arms. Topical testosterone treatments represented the most common treatment in the network, enrolling the most participants.

FIGURE 3.21: EVIDENCE NETWORK FOR LIBIDO, BY ROUTE OF ADMINISTRATION



There were no significant differences in libido between any route of administration and placebo, and there were no significant differences among the routes (Table 3.39).

TABLE 3.39: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION

	Standardized mean difference (standard deviation)			
	Placebo	Topical	IM	Oral
Topical	0.18 (1.30)	—		
IM	0.27 (2.58)	0.10 (2.88)	—	
Oral	1.70 (1.50)	1.52 (1.98)	1.42 (2.99)	—
Note: IM = intramuscular.				

TOTAL TESTOSTERONE LEVEL

Fifty trials reported serum total testosterone levels at the end of treatment (13, 14, 19-25, 28-33, 35-38, 40-50, 52-62, 64, 66-73). Of these, 46 provided data suitable for inclusion in the base-case analysis; 4 were excluded because they did not report sufficient data for analysis (1 trial reported values for the testosterone group only (73), 3 reported mean change only (35, 45, 67)). An additional 5 trials were excluded from the by-route analysis because each study arm involved the same route of administration (e.g., IM compared to IM) (46, 52, 53, 64, 71). The network thus comprised evidence from 41 trials involving 4 different routes of testosterone administration, with a total of 3608 participants (Figure 3.22). The network included 63 comparisons based on 39 trials comparing 2 routes and 2 trials comparing 3 routes. The network meta-analysis based on this evidence network was consistent (Appendix 6).

Compared with placebo, topical and intramuscular testosterone significantly increased total testosterone level at the end of the treatment period (Table 3.40). There was no significant difference between the treatment group and placebo for either oral testosterone or testosterone pellets. Among the treatments, intramuscular and topical were associated with significantly higher testosterone levels compared with oral testosterone (Table 3.40).

FIGURE 3.22: EVIDENCE NETWORK FOR TOTAL TESTOSTERONE LEVEL, END OF TREATMENT, ROUTE OF ADMINISTRATION

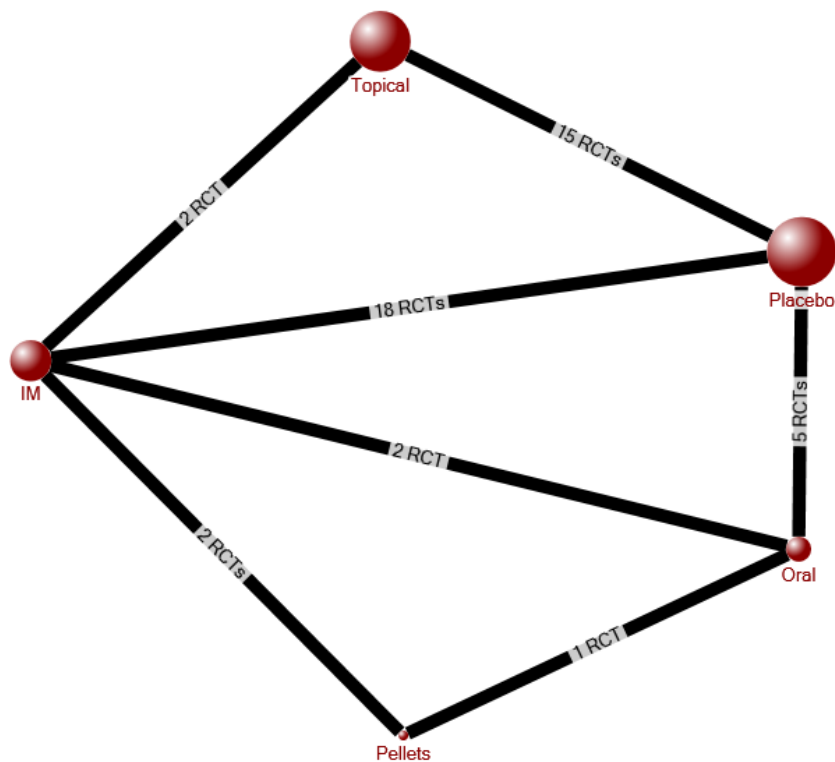


TABLE 3.40: TOTAL TESTOSTERONE LEVEL, END OF TREATMENT — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, BY ROUTE OF ADMINISTRATION

	Mean difference (standard deviation)				
	Placebo	Topical	IM	Oral	Pellets
Topical	9.73* (0.94)	—			
IM	7.11* (1.07)	2.63 (1.34)	—		
Oral	2.90 (1.59)	−4.21* (1.90)	−6.84* (1.72)	—	
Pellets	4.17 (3.07)	−2.94 (3.23)	−5.57 (3.00)	1.27 (3.14)	—

Note: IM = intramuscular.

* $p < 0.05$.

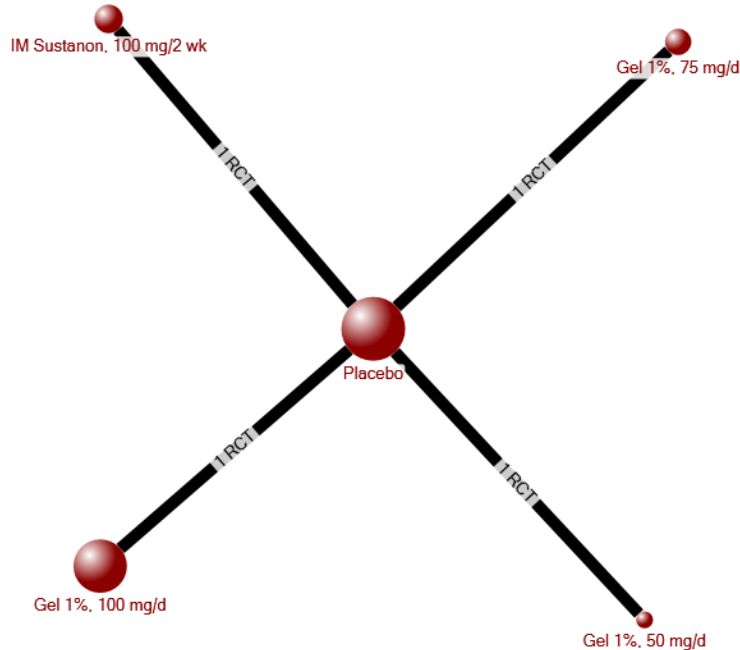
TREATMENT DURATION

DEPRESSION

LESS THAN 6 MONTHS

Of the 12 trials that evaluated the effect of testosterone replacement therapy on depressive symptoms, 5 trials involved a treatment duration of less than 6 months (24, 27, 28, 31, 32). Three trials had a treatment duration of 12 weeks (24, 27, 32), 1 had a duration of 14 weeks (28), and 1 had a duration of 24 weeks (31). The trial by Dobs and colleagues (31) could not be included in the network meta-analysis because its treatments were disconnected from the network (IM TE 200 mg/2 wk v. patch 5 mg/d). The network thus included 4 trials ranging in duration from 12 to 14 weeks and involved 225 participants (Figure 3.23). Four treatments were compared in the network, giving 4 comparisons based on 4 trials each with 2 arms.

FIGURE 3.23: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS WITH A TREATMENT DURATION OF LESS THAN 6 MONTHS



There were no significant differences in depression between placebo and any of the treatments or among the treatments in the network based on trials that involved treatment for less than 6 months (Table 3.41).

TABLE 3.41: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS

	Standardized mean difference (standard deviation)				
	Placebo	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	IM Sustanon 100 mg/2wk
Gel 1% 50 mg/d	0.01 (2.95)	—			
Gel 1% 75 mg/d	−0.62 (2.93)	−0.63 (4.15)	—		
Gel 1% 100 mg/d	−0.10 (2.90)	−0.10 (4.15)	0.52 (4.15)	—	
IM Sustanon 100 mg/2wk	0.55 (2.91)	0.54 (4.15)	1.17 (4.15)	0.65 (4.12)	—

Note: IM = intramuscular.

SIX MONTHS OR LONGER

Seven trials involved a treatment duration of 6 months or longer (13, 14, 19, 29, 30, 33, 34). The treatment duration was 6 months in 3 trials (13, 14, 30), 30 weeks in 2 studies (29, 34), 1 year in 1 trial (33), and 3 years in 1 trial (19). The network included all 7 trials, with a total of 766 participants (Figure 3.24). Five treatments were compared, giving 7 comparisons based on 7 trials each with 2 arms.

Compared with placebo, oral testosterone (160 mg/d; testosterone-based [T-based] dose 120 or 160 mg/d]) and intramuscular testosterone enanthate (200 mg/2 wk) significantly improved depressive symptoms (Table 3.42). Among the treatments, oral testosterone undecanoate at 2 doses (160 mg/dl; T-based dose) was significantly better than intramuscular testosterone undecanoate (1000 mg/12 wk) and intramuscular testosterone enanthate (300 mg/3 wk).

FIGURE 3.24: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS

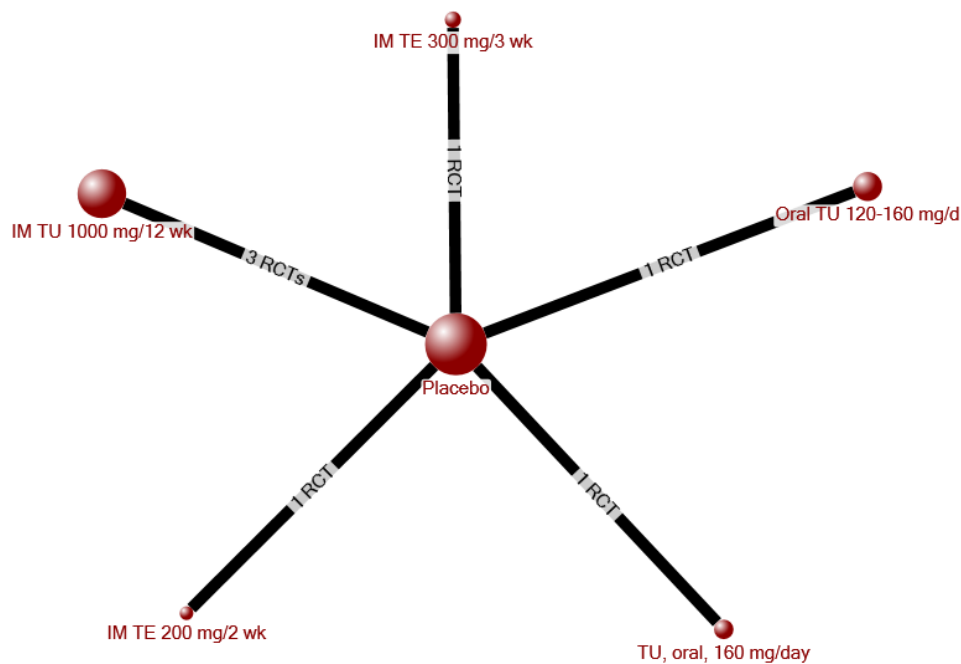


TABLE 3.42: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS OR LONGER

	Standardized mean difference (standard deviation)					
	Placebo	Oral TU, T-based dose	Oral TU 160 mg/d	IM TU 1000 mg/12 wk	IM TE 200 mg/2 wk	IM TE 300 mg/3 wk
Oral TU, T-based dose*	-3.52 [†] (0.92)	—				
Oral TU 160 mg/d	-2.63 [†] (0.91)	0.88 (1.29)	—			
IM TU 1000 mg/12 wk	-0.10 (0.51)	3.42 (1.05) [†]	2.54 [†] (1.04)	—		
IM TE 200 mg/2 wk	-1.76 [†] (0.93)	1.75 (1.30)	0.87 (1.30)	-1.67 (1.06)	—	
IM TE 300 mg/3 wk	-0.21 (0.94)	3.31 (1.32) [†]	2.43 [†] (1.30)	-0.11 (1.06)	1.56 (1.32)	—

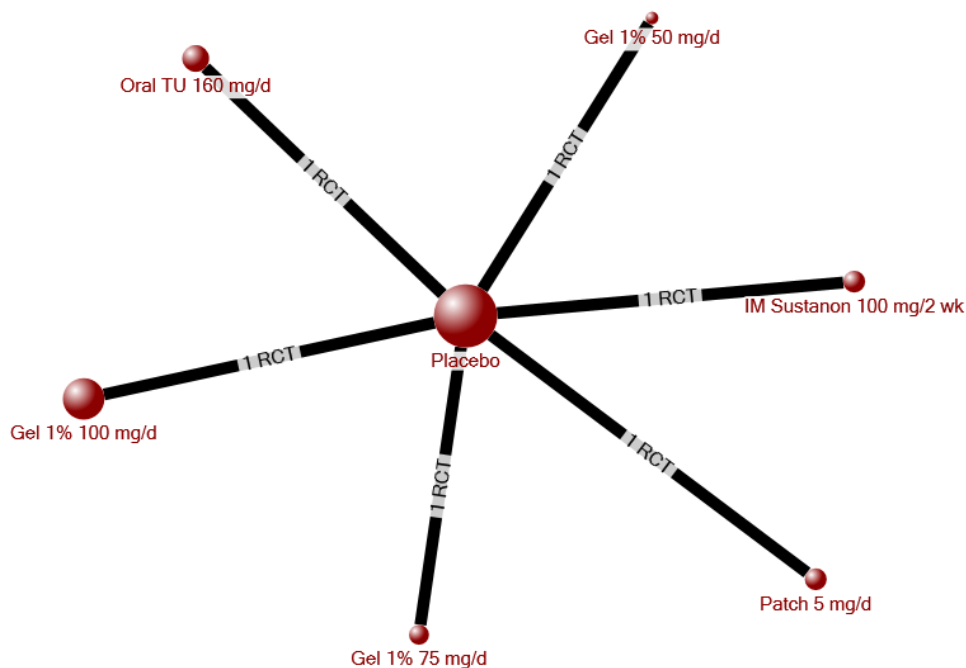
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
 *Dose of oral TU depended on baseline total T level. Patients with total testosterone < 8 nmol/L received 160 mg/d; patients with total testosterone between 8 and 12 nmol/L received 120 mg/d.
[†]*p* < 0.05

QUALITY OF LIFE

LESS THAN 6 MONTHS

Of the 21 trials that reported quality of life after testosterone replacement therapy, 7 involved a treatment duration of less than 6 months (24, 27, 28, 32, 41, 44, 46). The treatment duration was 12 weeks in 4 trials (24, 27, 32, 44), 14 weeks in 1 trial (28), and 16 weeks in 2 trials (41, 46). The trial by Hohl and colleagues (46) was excluded from the network because the treatments did not connect through a common comparator (IM TU 1000 mg/12 wk v. IM TC 200 mg/4 wk v. Durateston 250 mg/4wk). The network thus comprised 6 trials involving a total of 324 participants (Figure 3.25). The network compared 4 treatments, with the most common comparator being 1% testosterone gel. Six comparisons were made, based on 6 trials each with 2 arms.

FIGURE 3.25: EVIDENCE NETWORK FOR QUALITY OF LIFE AMONG TRIALS WITH A TREATMENT DURATION OF LESS THAN 6 MONTHS



Compared with placebo, there were no significant differences in quality of life among any of the trials with a treatment duration of less than 6 months, and there were no significant differences among the treatments (Table 3.43).

TABLE 3.43: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS

	Standardized mean difference (standard deviation)						
	Placebo	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	Oral TU 160 mg/d	IM Sustanon 100 mg/2 wk
Patch 5 mg/d	−0.50 (2.90)	—					
Gel 1% 50 mg/d	0.15 (2.95)	0.64 (4.14)	—				
Gel 1% 75 mg/d	0.26 (2.93)	0.76 (4.14)	0.11 (4.17)	—			
Gel 1% 100 mg/d	−0.05 (2.90)	0.44 (4.09)	−0.20 (4.14)	−0.32 (4.14)	—		
Oral TU 160 mg/d	−0.28 (2.93)	0.21 (4.13)	−0.43 (4.16)	−0.54 (4.14)	−0.23 (4.14)	—	
IM Sustanon 100 mg/2 wk	0.38 (2.93)	0.87 (4.13)	0.23 (4.16)	0.12 (4.13)	0.43 (4.14)	0.66 (4.14)	—

Note: IM = intramuscular, TU = testosterone undecanoate.

SIX MONTHS OR LONGER

Thirteen trials involved a treatment duration of 6 months or longer (13, 21, 29, 34, 36-40, 42, 43, 45, 47). The treatment duration was 6 months in 6 trials (13, 21, 40, 42, 45, 47), 30 weeks in 2 trials (29, 34), 48 weeks in 1 trial (37), and 1 year in 4 trial (36, 38, 39, 43). The network comprised all 13 trials and included a total of 2254 participants and 9 treatments (Figure 3.26). The network involved 15 comparisons, based on 12 trials with 2 arms and 1 trial with 3 arms. There was no evidence of inconsistency in this network (Appendix 6).

Compared with placebo, there were no significant differences in quality of life among trials of 6 months or longer, and there were no differences among the treatments (Table 3.44).

FIGURE 3.26: EVIDENCE NETWORK FOR QUALITY OF LIFE AMONG STUDIES WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS

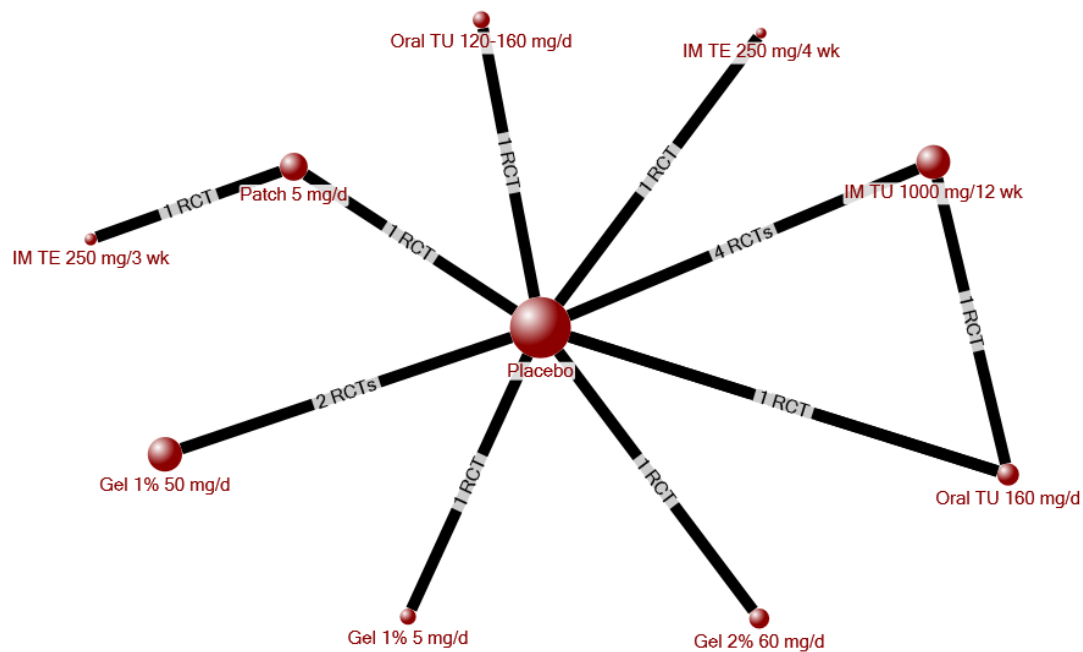


TABLE 3.44: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS OR LONGER

	Standardized mean difference (standard deviation)									
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 2%, 60 mg/d	TU, oral, 160 mg/d	Oral TU, T-based dose*	IM TU, 1000 mg/12 wk	IM TE, 250 mg/3 wk	IM TE, 250 mg/4 wk
Patch, 5 mg/d	-1.10 (1.44)	—								
Gel 1%, 5 mg/d	-0.36 (1.41)	0.75 (2.02)	—							
Gel 1%, 50 mg/d	-0.29 (0.98)	0.81 (1.74)	0.06 (1.72)	—						
Gel 2%, 60 mg/d	-0.12 (1.39)	0.98 (2.00)	0.24 (1.99)	0.18 (1.71)	—					
Oral TU, 160 mg/d	0.52 (0.95)	1.62 (1.72)	0.88 (1.70)	0.81 (1.36)	0.64 (1.68)	—				
Oral TU, T-based dose*	-1.96 (1.40)	-0.86 (2.00)	-1.61 (1.98)	-1.67 (1.71)	-1.84 (1.98)	-2.48 (1.69)	—			
IM TU, 1000 mg/12 wk	-0.78 (0.69)	0.32 (1.59)	-0.43 (1.57)	-0.49 (1.21)	-0.66 (1.56)	-1.30 (1.05)	1.18 (1.56)	—		
IM TE, 250 mg/3 wk	2.42 (2.01)	3.53 (1.40)	2.78 (2.46)	2.72 (2.24)	2.54 (2.44)	1.90 (2.22)	4.39 (2.45)	3.21 (2.13)	—	
IM TE, 250 mg/4 wk	-0.09 (1.41)	1.01 (2.01)	0.26 (1.99)	0.20 (1.72)	0.02 (1.99)	-0.61 (1.69)	1.87 (1.98)	0.69 (1.57)	-2.52 (2.46)	—

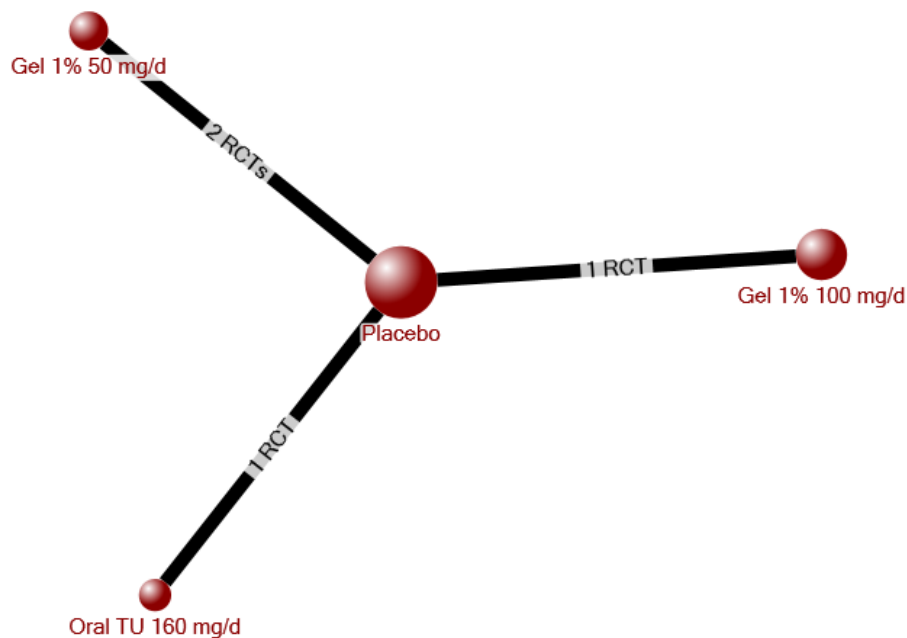
Note : IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
 *Dose of oral TU depended on baseline total testosterone level. Patients with total testosterone < 8 nmol/L received 160 mg/d; patients with total testosterone between 8 and 12 nmol/L received 120 mg/d.

ERECTILE FUNCTION

LESS THAN 6 MONTHS

Of the 10 trials that assessed the effect of testosterone replacement therapy on erectile function, 4 involved a treatment duration of less than 6 months (28, 41, 48, 49). The treatment duration was 3 months in 2 trials (48, 49), 14 weeks in 1 trial (28), and 4 months in 1 trial (41). Three treatments were compared in the network (Figure 3.27). The comparison between placebo and 1% gel 50 mg/d involved the most RCTs ($k = 2$) but more participants were involved in the 1% gel 100 mg/d arm (Figure 3.27). The total number of participants included in this network was 278. Four comparisons were made, based on 4 trials each with 2 arms.

FIGURE 3.27: EVIDENCE NETWORK FOR ERECTILE FUNCTION AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS



There were no significant differences in erectile function between placebo and any of the treatments among trials lasting less than 6 months, and there were no significant differences among the treatments (Table 3.45).

TABLE 3.45: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS

	Standardized mean difference (standard deviation)			
	Placebo	Gel 1% 50 mg/d	Gel 1% 100 mg/d	Oral TU 160 mg/d
Gel 1% 50 mg/d	0.54 (1.40)	—		
Gel 1% 100 mg/d	0.23 (1.98)	−0.31 (2.43)	—	
Oral TU 160 mg/d	−0.01 (1.99)	−0.56 (2.43)	−0.24 (2.80)	—

Note: TU = testosterone undecanoate.

SIX MONTHS OR LONGER

Six trials involved a treatment duration of 6 months or longer (14, 29, 34, 36, 37, 47). The treatment duration was 6 months in 2 trials (14, 47), 30 weeks in 2 trials (29, 34), 48 weeks in 1 study (37), and 1 year in 1 trial (36). The network involved 3 treatments, with the intramuscular testosterone undecanoate 1000 mg/12 wk node having the most participants (Figure 3.28). Eight comparisons were made in the network, based on 5 trials with 2 arms and 1 trial with 3 arms.

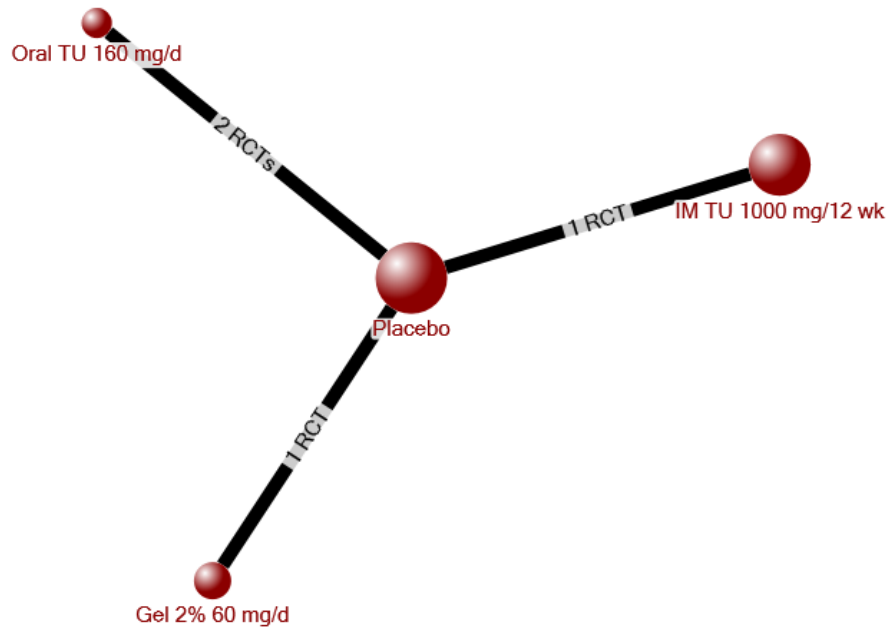
Compared with placebo, there were no significant differences in erectile function for any treatments compared in trials lasting 6 months or longer, and there were no significant differences among the treatments (Table 3.46).

TABLE 3.46: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS AND LONGER

	Standardized mean difference (standard deviation)			
	Placebo	Gel 2% 60 mg/d	Oral TU 160 mg/d	IM TU 1000 mg/12 wk
Gel 2% 60 mg/d	0.08 (1.06)	—		
Oral TU 160 mg/d	0.56 (0.75)	0.48 (1.30)	—	
IM TU 1000 mg/12 wk	0.34 (0.53)	0.26 (1.19)	−0.22 (0.82)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.

FIGURE 3.28: EVIDENCE NETWORK FOR ERECTILE FUNCTION AMONG TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS

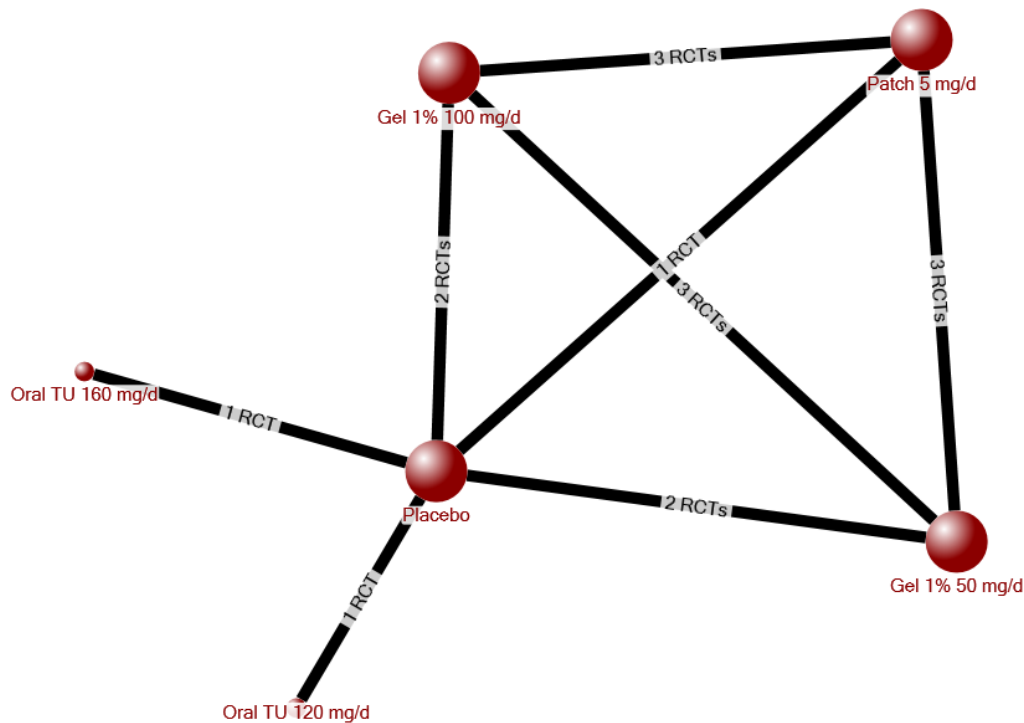


LIBIDO

LESS THAN 6 MONTHS

Of the 10 trials that assessed the effect of testosterone replacement therapy on libido, 7 involved a treatment duration of less than 6 months (28, 41, 48, 50, 52-54). The treatment duration was 3 months in 5 trials (48, 50, 52-54), 14 weeks in 1 trial (28), and 4 months in 1 trial (41). The network for libido included 5 treatments, with most patients receiving a topical testosterone treatment (Figure 3.29). The total number of participants was 1127, and 16 comparisons were made in the network, based on 4 trials with 2 arms, 2 trials with 3 arms, and 1 trial with 4 arms. The network appeared to be consistent (Appendix 6).

FIGURE 3.29: EVIDENCE NETWORK FOR LIBIDO AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS



Compared with placebo, 1% testosterone gel (100 mg/d) was more effective at improving libido (Table 3.47). There were no differences in libido between placebo and any of the other testosterone replacement therapies. Among the treatments, 1% testosterone gel (100 mg/d) was more effective than testosterone patch (5 mg/d) and oral testosterone undecanoate (160 mg/d). Oral testosterone undecanoate at 120 mg/d was more effective than oral testosterone undecanoate at 160 mg/d.

TABLE 3.47: LIBIDO — HEAD-TO-HEAD COMPARISONS OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION LESS THAN 6 MONTHS

	Standardized mean difference (standard deviation)					
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral TU, 120 mg/d	Oral TU, 160 mg/d
Patch, 5 mg/d	0.05 (0.16)	—				
Gel 1%, 50 mg/d	0.11 (0.15)	0.06 (0.13)	—			
Gel 1%, 100 mg/d	0.32* (0.14)	0.27* (0.13)	0.21 (0.12)	—		
Oral TU, 120 mg/d	0.45 (0.34)	0.40 (0.38)	0.34 (0.37)	0.13 (0.37)	—	
Oral TU, 160 mg/d	−0.53 (0.32)	−0.58 (0.35)	−0.64 (0.35)	−0.85* (0.34)	−0.98* (0.47)	—
Note: TU = testosterone undecanoate. * $p < 0.05$						

SIX MONTHS OR LONGER

Three trials involved a treatment duration of 6 months or longer (14, 34, 36). Each trial involved a different treatment duration: 6 months (14), 30 weeks (34), or 12 months (36). Three treatments were included in the network (504 participants), and the network comprised 3 comparisons, based on 3 trials each with 2 arms (Figure 3.30).

There were no significant differences in libido between placebo and any of the included testosterone replacement therapies, and there were no significant differences among the treatments (Table 3.48).

FIGURE 3.30: EVIDENCE NETWORK FOR LIBIDO INVOLVING TRIALS WITH A TREATMENT DURATION OF AT LEAST 6 MONTHS

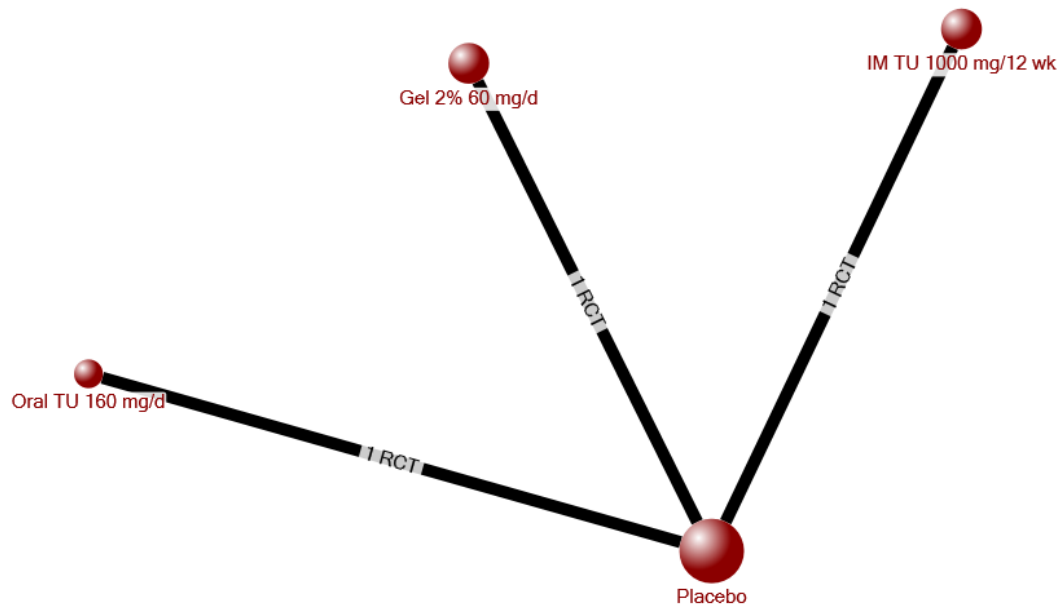


TABLE 3.48: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, TREATMENT DURATION 6 MONTHS AND LONGER

	Standardized mean difference (standard deviation)			
	Placebo	Gel 2% 60 mg/d	Oral TU 160 mg/d	IM TU 1000 mg/12 wk
Gel 2% 60 mg/d	0.21 (2.90)	—		
Oral TU 160 mg/d	5.25 (2.94)	5.03 (4.14)	—	
IM TU 1000 mg/12 wk	0.29 (2.90)	0.07 (4.11)	−4.96 (4.13)	—

Note: IM = intramuscular, TU = testosterone undecanoate.

AGE

In general, there were limited data available for analysis by age (< v. ≥ 65 years) because most trials included a broad range of participants. The results of the analyses presented below should be interpreted with caution because the findings are based on limited data.

DEPRESSION

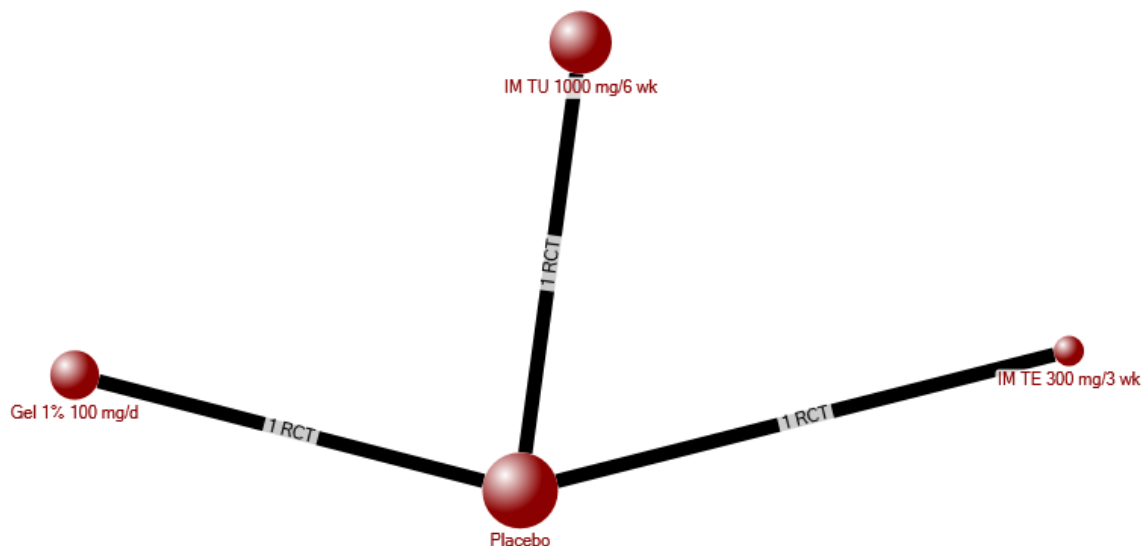
Of the 12 trials that reported the effect of testosterone replacement therapy on depression, 4 trials involved patients under 65 years (28-31), and 1 trial involved men aged 65 years and older (19) (Table 3.50).

AGE LESS THAN 65 YEARS

Three trials were included in the network meta-analysis of the effect of testosterone on depressive symptoms among patients aged less than 65 years (28-30). The trial by Dobs and colleagues (31) was excluded from the network meta-analysis because the treatments involved did not connect to the network through a common comparator (patch 5 mg/d v. IM TE 200 mg/2 wk). The duration of the included trials was between 14 and 30 weeks.

The evidence network for the effect for this outcome included 376 participants (Figure 3.31). Three treatments were included in the network, providing 3 comparisons based on 3 trials each with 2 arms.

FIGURE 3.31: EVIDENCE NETWORK FOR DEPRESSION INVOLVING TRIALS INVOLVING MEN AGED YOUNGER THAN 65 YEARS



There were no significant differences in depressive symptoms between placebo and any of the treatments among the trials that involved men aged less than 65 years, and there were no differences among the treatments (Table 3.49).

TABLE 3.49: DEPRESSION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS

	Standardized mean difference (standard deviation)			
	Placebo	Gel 1% 100 mg/d	IM TU 1000 mg/6 wk	IM TE 300 mg/3 wk
Gel 1% 100 mg/d	−0.10 (2.90)	—		
IM TU 1000 mg/6 wk	−0.18 (2.89)	−0.07 (4.10)	—	
IM TE 300 mg/3 wk	−0.20 (2.92)	−0.10 (4.12)	−0.02 (4.13)	—
Note: IM = intramuscular, TE = testosterone undecanoate, TU = testosterone undecanoate.				

AGE 65 YEARS AND OLDER

Because only 1 trial involved men over the age of 65 years (19), network meta-analysis was not possible. In the trial by Amory and colleagues (19), the mean age of participants was 71 (SD 4) years. The authors reported a significant improvement in depressive symptoms among men taking testosterone enanthate (IM 200 mg/2wk) compared with men taking placebo (Table 3.50). The authors comment that antidepressant use did not differ between the 2 groups; however, 29% of men (6/21) in the testosterone group were taking an antidepressant compared with 11% in the placebo group (2/18).

TABLE 3.50: CHARACTERISTICS OF TRIALS THAT ASSESSED DEPRESSION, BY AGE

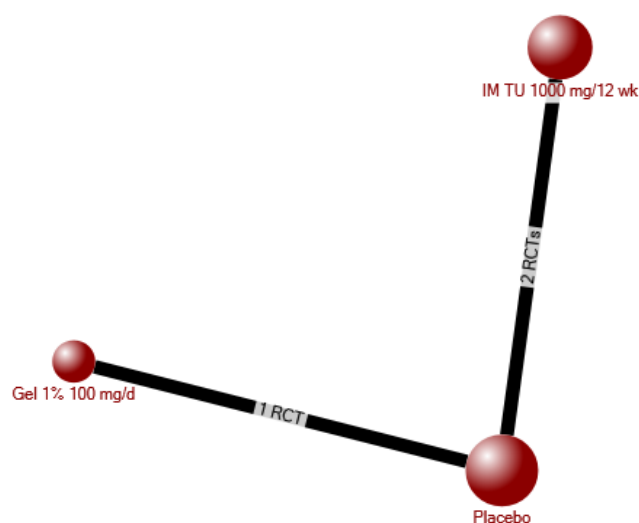
Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr, mean (SD)	Score, mean (SD)		Significant in original study	Comments
							Before	After		
< 65 yr										
Spitzer 2012	Erectile dysfunction	GWBI, depressed mood domain	Lower score indicates worse depression*	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	86 (14.9) 86 (14.9)	83 (19) 85 (19)	No	Patients in both groups were also taking sildenafil; Antidepressant use NR
Kalinchenko 2010	MetS	BDI	Higher scores indicates worse depression	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.7) 51.6 (9.8)	9.1 (8.2) 9.7 (8.9)	7.2 (6.6) 6.1 (5.9)	No†	Patients with major depression taking antidepressants were excluded; 60% in each group had moderate to severe depressive symptoms
Dobs 1999	Receiving TRT for at least 3 mo	BDI	Higher scores indicates worse depression	24	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	4.8 (5.7) 4.7 (4.2)	3.9 (5.7) 4.9 (4.2)	No	Patients with clinically significant psychiatric disease, antidepressant use or antipsychotic therapy were excluded. 4 to 6 wk washout period was used before baseline
Grinspoon 1998	AIDS wasting syndrome	BDI	Higher scores indicates worse depression	26	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	13.4 (8.2) 15 (7.7)	10.8 (8.2) 9.2 (7.1)	No	Antidepressant use NR
≥ 65 yr										
Amory 2004	T below the range of normal for young adult men	BDI	Higher scores indicates worse depression	156	Placebo (24) IM TE, 200 mg/2 wk (24)	71 (4) 71 (4)	5.1 (1.0) 3.3 (0.6)	4.8 (1.0) 3.2 (0.6)	Yes	“Antidepressant use did not differ between treatment groups either at baseline (6 of 21 testosterone-treated vs. 2 of 18 placebo-treated patients”
Note: BDI = Beck Depression Index, ED = erectile dysfunction, GWBI = General Well-Being Index, HADS-D = Hospital Anxiety and Depression score, depression domain, HAM-D = Hamilton Rating Scale for Depression, HDMS = Hamilton Depression and Melancholia Scale, IM = intramuscular injection, NR = not reported, SD = standard deviation, T = testosterone, TC = testosterone cypionate TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate. *Direction of the data was reversed before analysis †Authors reported significance after adjustment but rationale for adjustment not provided.										

QUALITY OF LIFE

AGE LESS THAN 65 YEARS

Four trials assessed quality of life among men aged less than 65 years (28, 29, 37, 43); however, 1 trial (43) was excluded from the network meta-analysis because its treatments did not connect through a common comparator (patch 4.8 mg/d v. IM TE 250 mg/3wk) (Table 3.53). The network included 2 treatments, and a total of 444 participants (Figure 3.32). Three comparisons were made, based on 3 trials each with 2 arms.

FIGURE 3.32: EVIDENCE NETWORK FOR QUALITY OF LIFE INVOLVING MEN AGED LESS THAN 65 YEARS



There were no significant differences between either treatment and placebo among men aged less than 65 years, and there was no difference between the 2 treatments (Table 3.51).

TABLE 3.51: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS

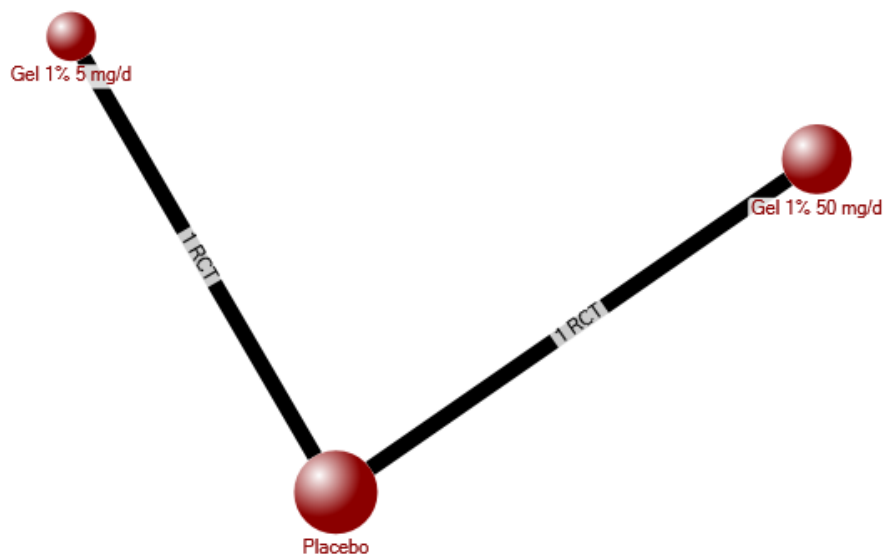
	Standardized mean difference (standard deviation)		
	Placebo	Gel 1% 100 mg/d	IM TU 1000 mg/12 wk
Gel 1% 100 mg/d	−0.04 (1.94)	—	
IM TU 1000 mg/12	−0.27 (1.37)	−0.23 (2.38)	—

Note: IM = intramuscular, TU = testosterone undecanoate.

AGE 65 YEARS AND OLDER

Two trials assessed quality of life among men aged 65 years and older (38, 40). The network comprised 2 treatments, and involved 405 participants. Two comparisons were made based on 2 trials each with 2 arms (Figure 3.33).

FIGURE 3.33: EVIDENCE NETWORK FOR QUALITY OF LIFE INVOLVING MEN AGED 65 YEARS AND OLDER



There were no significant differences between either of the treatments and placebo or among the treatments in quality of life among patients aged 65 years and older (Table 3.52).

TABLE 3.52: QUALITY OF LIFE — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED 65 YEARS AND OLDER

	Standardized mean difference (standard deviation)		
	Placebo	Gel 1% 5 mg/d	Gel 1% 50 mg/d
Gel 1% 5 mg/d	−0.37 (2.89)	—	
Gel 1% 50 mg/d	−0.31 (2.86)	0.06 (4.10)	—

TABLE 3.53: CHARACTERISTICS OF TRIALS THAT ASSESSED QUALITY OF LIFE, BY AGE

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr, mean (SD)	Score, mean (SD)		Significant in original study
							Before	After	
< 65 yr									
Spitzer 2012	Erectile dysfunction	MEDQoL	Higher score indicates improved QoL*	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	62 (25.6) 56 (27.4)	69 (25.6) 66 (27.7)	No
Ho 2011	At least mild AMS symptoms	AMS	Higher score indicates worse QoL	48	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	38.46 (11.85) 41.73 (12.73)	33.59 (10.69) 32.61 (9.67)	No
Kalinchenko 2010	MetS	AMS	Higher score indicates worse QoL	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.7) 51.6 (9.8)	42.3 (12.0) 44.3 (11.9)	37.6 (12.5) 32.2 (12.2)	Yes
Raynaud 2008	Hypogonadal men	AMS	Higher score indicates worse QoL	53	Patch, 4.8 mg/d (188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	37.5 (0.9) 40 (2.5)	30 (1.1) 35 (2.5)	Yes
≥ 65 yr									
Kenny 2010	Low bone mass and physical frailty	IPSS, QoL domain	Higher score indicates worse QoL	52	Placebo (62) Gel 1%, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	3.1 (1.3) 2.7 (1.3)	3.0 (1.5) 2.5 (1.3)	Yes
Srinivas- Shankar 2010	Intermediate-frail and frail	AMS, sexual function domain	Higher score indicates worse QoL	26	Placebo (136) Gel 1%, 50 mg/d (138)	73.7 (5.7) 73.9 (6.4)	13.8 (4.5) 13.7 (4.3)	12.3 (4.6) 10.9 (4.5)	Yes

Note: AMS = Aging Males Symptoms, IM = intramuscular, IPSS = International Prostate Symptom Score, MEDQoL = MED Quality of Life, MetS = metabolic syndrome, QoL = quality of life, SD = standard deviation, TE = testosterone enanthate, TU = testosterone undecanoate.

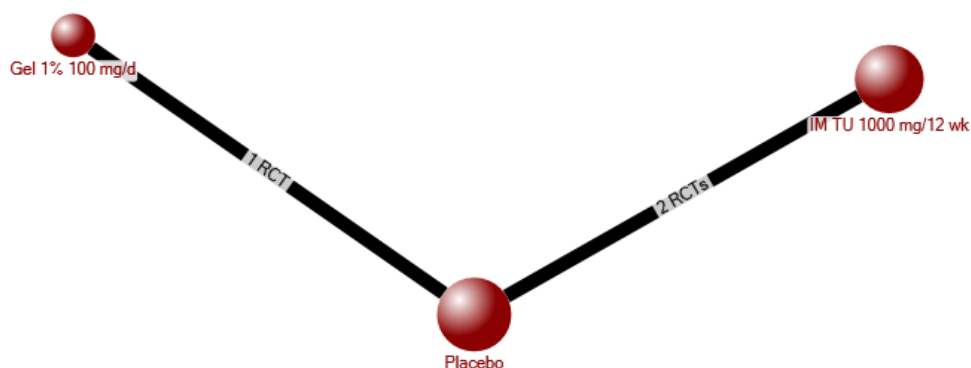
*The direction of this scale was reversed before analysis.

ERECTILE FUNCTION

AGE LESS THAN 65 YEARS

Three trials assessed erectile function among men aged less than 65 years (28, 29, 37) (Table 3.55). The network meta-analysis for erectile function in this population included 2 treatments and a total of 444 participants (Figure 3.34). Three comparisons were made, based on 3 trials each with 2 arms.

FIGURE 3.34: EVIDENCE NETWORK FOR ERECTILE DYSFUNCTION AMONG MEN AGED LESS THAN 65 YEARS



Among men aged less than 65 years, there were no significant differences in erectile function between placebo and either treatment or among the treatments (Table 3.54).

TABLE 3.54: ERECTILE FUNCTION — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG PATIENTS AGED LESS THAN 65 YEARS

	Standardized mean difference (standard deviation)		
	Placebo	Gel 1% 100 mg/d	IM TU 1000 mg/12 wk
Gel 1% 100 mg/d	0.23 (1.87)	—	
IM TU 1000 mg/12 wk	0.14 (1.32)	−0.09 (2.29)	—

Note: IM = intramuscular, TU = testosterone undecanoate.

AGE 65 YEARS AND OLDER

No trials were identified that included participants aged 65 years and older and assessed erectile function following testosterone replacement therapy.

TABLE 3.55: CHARACTERISTICS OF TRIALS THAT ASSESSED ERECTILE FUNCTION, BY AGE

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study*	Comments
							Before	After		
< 65										
Spitzer 2012	Erectile dysfunction	IIEF, EF domain	Higher score indicates improved function	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	20 (8.5) 19 (8.5)	19 (14.9) 21 (8.5)	No	All men had ED at baseline; patients in both groups were taking sildenafil on demand
Ho 2011	At least mild AMS symptoms	IIEF-5	Higher score indicates improved function	48	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	15.55 (5.8) 14.3 (6.2)	16.5 (6.0) 16.5 (5.9)	No	ED at baseline: 24% Placebo group; 18% TRT group; ED medication use not reported
Kalinchenko 2010	MetS	IIEF-5	Higher score indicates improved function	30	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	14.1 (7.3) 13.0 (7.3)	14.5 (7.3) 16.5 (7.3)	No	Prevalence of ED and ED medication use not reported at baseline
≥ 65										
No trials identified										

Note: AMS = Aging Males Symptoms, EF = erectile function, ED = erectile dysfunction, IIEF = International Index of Erectile Function, IM = intramuscular injection, MetS = metabolic syndrome, TU = testosterone undecanoate.

*Based on difference in means between groups after treatment.

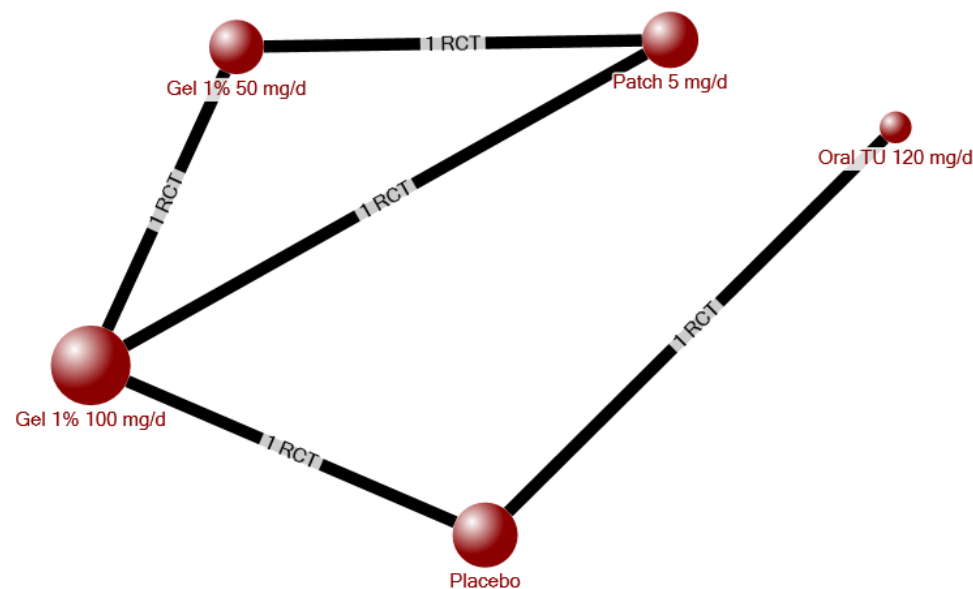
LIBIDO

AGE LESS THAN 65 YEARS

Three trials assessed libido among men aged less than 65 years (28, 50, 53) (Table 3.57). The standard deviation of the mean age was not reported in 1 trial (53); however, we felt that the mean age plus 1 standard deviation would be less than 65 years based on comparable ages reported by the other 2 trials (28, 50).

The network for libido among men aged less than 65 years included 5 comparisons, based on 2 trials with 2 arms and 1 trial with 3 arms (Figure 3.35). Four treatments were included in the network, with a total of 415 participants.

FIGURE 3.35: EVIDENCE NETWORK FOR LIBIDO AMONG MEN AGED LESS THAN 65 YEARS



There were no significant differences between any of the treatments and placebo or among the treatments for libido among men aged less than 65 years (Table 3.56).

TABLE 3.56: LIBIDO — HEAD-TO-HEAD COMPARISON OF TESTOSTERONE REPLACEMENT THERAPIES, AMONG MEN AGED LESS THAN 65 YEARS

	Standardized mean difference (standard deviation)				
	Placebo	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 100 mg/d	Oral TU 120 mg/d
Patch 5 mg/d	−0.09 (4.05)	—			
Gel 1% 50 mg/d	0.03 (4.07)	0.12 (2.91)	—		
Gel 1% 100 mg/d	0.12 (2.85)	0.21 (2.87)	0.09 (2.91)	—	
Oral TU 120 mg/d	0.46 (2.90)	0.55 (4.97)	0.43 (4.98)	0.33 (4.07)	—

Note: TU = testosterone undecanoate.

AGE 65 YEARS AND OLDER

No trials were identified that investigated the effect of testosterone replacement therapy on libido among men aged 65 years and older.

TABLE 3.57: CHARACTERISTICS OF TRIALS THAT ASSESSED LIBIDO, BY AGE

Trial	Population	Scale	Direction of scale	Duration, wk	Treatment (no. randomized)	Age, yr	Mean (SD)		Significant in original study*	Comments
							Before	After		
< 65 yr										
Spitzer 2012	Erectile dysfunction	MSHQ, sexual dysfunction domain	Higher score indicates improved libido	14	Placebo (70) Gel 1%, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	10.0 (3.2) 9.8 (3.2)	10.0 (3.2) 10.5 (4.3)	No	Participants in both groups were taking sildenafil on demand
Boyanov 2003	T2DM, obesity, and “symptoms of andropause or erectile dysfunction”	Subscale of PADAM questionnaire	Higher score indicates improved libido	12	No treatment (24) Oral TU, 120 mg/d (24)	57.5 (4.8) (not reported by group)	1.50 (1.0) 1.25 (1.0)	1.68 (1.25) 2.13 (0.61)	No	
Wang 2000	Primary, secondary or late-onset hypogonadism	7-point Likert scale	Higher score indicates improved libido	12	Patch 5 mg/d (76)	51.1 (NR)	2.0 (4.4)	2.7 (4.4)	• Gel 50 v. patch: No • Gel 100 v. patch: No • Gel 50 v. gel 100: No	Double blind for gels; open-label for patch
					Gel 1%, 50 mg/d (73)	51.3 (NR)	2.1 (4.3)	3.2 (4.3)		
					Gel 1%, 100 mg/d (78)	51.0 (NR)	1.9 (4.4)	3.6 (4.4)		
≥ 65 yr										
No trials identified										

Note: IIEF = International Index of Erectile Function, MSHQ = Male Sexual Health Questionnaire, PADAM = Partial Androgen Deficiency in Aging Men, PDQ = Psychosexual Daily Questionnaire, SD = standard deviation, T2DM = type 2 diabetes mellitus, TU = testosterone undecanoate.

*Based on difference in means between placebo and TRT group after treatment.

COMORBIDITIES

DIABETES MELLITUS

Two trials included men with diabetes mellitus (34, 50), and an additional 4 trials included men with diabetes or metabolic syndrome (23, 36, 47, 68) (Table 3.58). One trial included men with metabolic syndrome only (29).

Of the 2 trials that assessed participants with diabetes (34, 50), both assessed the effect of testosterone replacement therapy on erectile function. Hackett and colleagues reported a significant difference in erectile function between men taking intramuscular testosterone undecanoate (1000 mg/12 wk) and those receiving placebo after 30 weeks of treatment (Table 3.58).

Although Boyanov and colleagues (50) stated that they assessed erectile function using the IIEF-5 scale, the data presented in their table and text were not consistent with the use of this scale, and we did not include these data in our meta-analyses of erectile function. For example, the IIEF-5 includes 5 questions, each rated on a 5-point scale, giving a possible score ranging from 1 (severe ED) to 25 (no ED). The title of their results table reads “mean scores of symptoms of androgen deficiency and erectile function on a 4-point self-administered scale.” The mean (SD) values provided for the testosterone and placebo groups before treatment were 2.25 (0.675) and 2.50 (0.75) respectively, with after-treatment values of 1.06 (0.90) and 2.25 (0.875) respectively, suggesting that the score decreased in the testosterone group but not the placebo group. The authors described this change as indicating a shift from moderate to mild in the testosterone group. However, on the IIEF-5 scale, scores between 1 and 7 are considered to indicate severe erectile dysfunction, with higher scores indicating improvement in symptoms.

Hackett and colleagues (34) also reported no significant effect of testosterone replacement therapy on depression or quality of life, while Boyanov and colleagues (50) reported no significant effect on libido. Both trials reported a significantly higher total testosterone level in the treated group compared to the placebo group at the end of treatment.

DIABETES MELLITUS AND METABOLIC SYNDROME

Among the trials that included men with diabetes or metabolic syndrome (23, 36, 47, 68), 2 assessed quality of life and erectile function (36, 47), 1 assessed libido, and 4 assessed total testosterone level. All 4 trials reported a significant increase in total testosterone levels relative to placebo following treatment.

Jones and colleagues (36) and Aversa and colleagues (47) both reported no significant difference in erectile function between testosterone replacement therapy and placebo. Both trials also assessed quality of life: Jones and colleagues (36) reported no significant difference between treatment and control, while Aversa and colleagues (47) found no significant difference between placebo and oral testosterone, but they found a significant difference in quality of life between intramuscular testosterone (TU 1000 mg/12 wk).

Jones and colleagues (36) found no significant difference in libido between men who received testosterone gel (2%, 60 mg/d) or placebo.

METABOLIC SYNDROME

Kalinchenko and colleagues (29) reported a significant improvement in total testosterone level, quality of life, and depression following treatment with intramuscular testosterone undecanoate (1000 mg/12 wk). However, their finding of a significant effect on depression was based on an adjusted analysis (adjusted for age, body mass index, smoking status, total testosterone level, diabetes mellitus), with no rationale given for adjustment. There were no significant differences at baseline between the testosterone and placebo groups for age, total testosterone or diabetes, and the authors state that “Men randomly assigned to [testosterone undecanoate] did not differ statistically significantly for any of the socio-demographic, clinical, and laboratory measures at baseline.”

TABLE 3.58: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS OR METABOLIC SYNDROME

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Outcomes of interest	Significant in original study*
T2DM							
Hackett 2013	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	• Depression • QoL • ED • Total T	• No • No • Yes • Yes
Boyanov 2003	T2DM, obesity, and “symptoms of andropause or ED”	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	• ED • Libido • Total T	• NA† • No • Yes
MetS or T2DM							
Jones 2011	MetS or T2DM with ≥ 2 symptoms of hypogonadism	12 mo	Placebo (112) 2% gel, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	9.5 (3.3) 9.2 (2.6)	• QoL • ED • Libido • Total T	• No • No • No • Yes
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	• QoL • ED • Total T	• Oral v. placebo: no; IM v. placebo: yes • No (for all comparisons) • Oral v placebo: no; IM v. placebo: yes
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	• Total T	• Yes
Heufelder 2009	MetS and newly diagnosed diabetes	52 wk	Placebo (16) Gel 1%, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	• Total T	• Yes
Mets							
Kalinchenko 2010	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	• Depression • QoL • ED • Total T	• No‡ • Yes • No • Yes
Note: ED = erectile dysfunction, IM = intramuscular injection, MetS = metabolic syndrome, NR = not reported, QoL = quality of life, SD = standard deviation, T = testosterone, T2DM = type 2 diabetes mellitus, TU = testosterone undecanoate. *Based on difference in means between treatment groups after treatment. †Although Boyanov and colleagues stated that they assessed ED using the International Index of Erectile Function–5 scale, the data and interpretations were not consistent with the use of this scale. This trial was not included in our network meta-analysis for erectile function. ‡Authors report significant after adjustment but rationale for adjustment not provided.							

DEPRESSION

Two trials included participants with depression (24, 32). Shores and colleagues (24) included participants with dysthymia or minor depression, while Orengo and colleagues (32) included participants with treatment-resistant depression. Both trials involved treatment with topical 1% testosterone gel (Shores: 75 mg/d; Orengo: 50 mg/d).

Shores and colleagues (24) excluded men with schizophrenia, bipolar disorder, dementia, psychiatric instability, or suicidality. They also excluded men taking benzodiazepine or antipsychotics, and 3 men in each group were on stable antidepressant dosages at baseline. Orengo and colleagues (32) included men with treatment-resistant depression, and all men were taking antidepressants during the treatment period.

Neither trial reported a significant difference in depressive symptoms between the placebo and testosterone group at the end of treatment. Shores and colleagues (24) reported that there was a significant difference between groups after adjustment for age. Both trials found no significant difference in quality of life between the placebo and testosterone-treated participants. Shores and colleagues reported a significant increase in total testosterone level following treatment in the testosterone group; however, Orengo and colleagues (32) found no significant difference in testosterone level between the testosterone and placebo groups.

TABLE 3.59: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH DEPRESSION

Trials	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcomes of interest	Significant in original study*
Shores 2009	Dysthymia or minor depression	12 wk	Placebo (16) Gel 1%, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	• Depression • QoL • Total T	• No† • No • Yes
Orengo 2005	Treatment- resistant depression	12 wk	Placebo (5) Gel 1%, 50 mg/d (7)	All: 63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	• Depression • QoL • Total T	• No • No • No
Note: NR = not reported, QoL = quality of life, SD = standard deviation, T = testosterone. *Based on difference in means between placebo and TRT group after treatment. †Authors report significant after adjustment for age.							

OBESITY

One trials involved participants with obesity (50), defined by the authors as a waist-to-hip ratio greater than 0.9. Boyanov and colleagues (50) randomized 24 participants to no treatment, and 24 participants to receive oral testosterone undecanoate (120 mg/d) for 12 weeks (Table 3.60). Following treatment the total testosterone level was significantly higher in the testosterone-treated group than in the no-treatment group. There was no significant difference between the groups for libido. The authors report that libido was significantly

increased in the testosterone group; however, the data provided do not support this conclusion.

TABLE 3.60: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH OBESITY

Trials	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcomes of interest	Significant in original study*
Boyanov 2003	T2DM, visceral obesity, [†] and “symptoms of andropause or ED”	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	• ED • Libido • Total T	• NA [‡] • No • Yes

Note: ED = erectile dysfunction, NA = not applicable, NR = not reported, SD = standard deviation, T2DM = type 2 diabetes mellitus, T = testosterone.
 *Based on difference in means between placebo and testosterone groups after treatment.
 †Obesity was defined by Boyanov and colleagues as waist-hip ratio ≥ 0.9
 ‡Although Boyanov and colleagues stated that they assessed ED using the International Index of Erectile Function-5 scale, the data and interpretations were not consistent with the use of this scale. This trial was not included in our network meta-analysis for erectile function.

CORONARY ARTERY DISEASE

One trial included participants with coronary artery disease (63), and 3 trials included participants with other cardiovascular complaints [chronic heart failure (22, 27); chronic angina pectoris (57)] (Table 3.61).

Kang and colleagues (63) randomized 17 participants with coronary artery disease to placebo and 18 participants to oral testosterone undecanoate (160 mg/d) for 12 weeks. Their primary outcome was brachial arterial vasoreactivity following testosterone replacement therapy, and they reported none of our outcomes of interest.

Stout and colleagues (27) and Caminiti and colleagues (22) enrolled participants with chronic heart failure and both randomized participants to placebo or to an intramuscular form of testosterone (Stout: Sustanon 100 mg/2 wk; Caminiti: TU 1000 mg/12 wk) for 12 weeks. Stout and colleagues (27) found no significant differences between placebo and testosterone groups for depression and quality of life, while Caminiti and colleagues (22) reported that there was a significant increase in total testosterone in the testosterone group following treatment (Table 3.61).

Mathur and colleagues (57) randomized 7 participants with chronic angina pectoris to placebo and 8 to intramuscular testosterone undecanoate (1000 mg/12 wk) for 12 weeks. At

the end of the treatment period, participants in the testosterone treatment group had a significantly higher level of total testosterone compared to participants who had received placebo (Table 3.61).

TABLE 3.61: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH CORONARY ARTERY DISEASE

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcomes of interest	Significant in original study*
Coronary artery disease							
Kang 2002	Coronary artery disease	12 wk	Placebo (17) Andriol, oral, 160 mg/d (18)	58 (9) 57 (7)	Free T, pg/ml 13.8 (1.8) 9.9 (3.1)	NA	NA
Other coronary comorbidities							
Stout 2012	Chronic heart failure	12 wk	Placebo (20) Sustanon, 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	• Depression • QoL	• No • No
Caminiti 2009	Chronic heart failure	12 wk	Placebo (35) Nebido, IM, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	• Total T	• Yes
Mathur 2009	Chronic angina pectoris	12 mo	Placebo (7) Nebido, IM, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	• Total T	• Yes
Note: IM = intramuscular injection, NA = not applicable, QoL = quality of life, SD = standard deviation, T = testosterone. *Based on difference in means between placebo and testosterone groups after treatment.							

HYPERLIPIDEMIA

No trials were included that specifically enrolled participants with hyperlipidemia.

HYPERTENSION

No trials were included that specifically enrolled participants with hypertension.

3.4 DISCUSSION

3.4.1 SUMMARY

In our systematic review and network meta-analysis, we found that some testosterone replacement therapies significantly improved depression and quality of life; however, the effect varied depending on formulation, dose, and route of administration. We found no significant effect of testosterone replacement therapies on erectile function or libido. Most testosterone replacement products restored testosterone levels to the normal range by the end of the treatment period. These findings were based on all eligible studies and some were at high risk of bias.

In our previous network meta-analysis, we found no effect of Health Canada-approved testosterone replacement products on depression, quality of life, erectile function, or libido (74). The present analysis was not restricted to testosterone replacement products approved in Canada; this allowed the inclusion of more trials and more treatment arms. To the best of our knowledge, this is the first network meta-analysis of testosterone replacement therapy.

We found that 3 of 10 testosterone treatments improved depression relative to placebo and that oral testosterone was generally more effective than the other routes of administration for resolving depression. There were no significant differences between placebo and any of the treatments for quality of life, erectile function, and libido. In trials lasting for less than 6 months, testosterone 1% gel was significantly better than placebo, testosterone patch, and oral testosterone undecanoate at improving libido; however, there were no differences among the treatments investigated in trials lasting 6 months or longer. There were no differences by route of administration or length of treatment for quality of life or erectile function.

There were limited data with which to investigate the benefits of testosterone replacement therapy by participant age ($< v. \geq 65$ yr). Based on limited data, we found that there were no differences in quality of life among men who received any testosterone treatment and placebo among men aged less than 65 years or at least 65 years. There were no differences among the treatments for depression, erectile function, or libido among men aged less than

65 years. There were insufficient data to evaluate these outcomes among men aged 65 years and older. Because these findings are based on limited data, the findings should be interpreted with caution.

We did not have sufficient data to perform network meta-analysis for patient comorbidities (diabetes, obesity, depression, coronary artery disease, hypertension, hyperlipidemia).

3.4.2 CONTEXT

DEPRESSION

Of the 10 testosterone replacement products included in our evaluation of depression following treatment, we found that 3 products significantly resolved depressive symptoms compared with placebo (oral TU 160 mg/d, oral TU [T-based dose 120 or 160 mg/d], IM TE 200 mg/2wk). Among the treatments, oral testosterone undecanoate was significantly better than most other treatments. In our previous analysis involving Health Canada–approved testosterone products, we found no significant differences between the included testosterone products and placebo; however, in our subgroup analyses, we found that the oral testosterone products were significantly better than placebo and the intramuscular and topical products (74).

A 2014 meta-analysis of placebo-controlled RCTs involving men with depression or normal mood found a significant effect of testosterone (any testosterone v. placebo) on depression among hypogonadal men but not eugonadal men (8). There were important differences between our review and that by Amanatkar and colleagues (8). First, Amanatkar and colleagues (8) included trials of all durations, whereas we included only trials lasting at least 12 weeks. Second, 1 trial included in the present analysis were not included in the analysis by Amanatkar and colleagues (8) because they used a “different scale” (14), although it is not clear why this scale was excluded. Third, because we performed a network meta-analysis, we were able to include trials that had an active control group, while Amanatkar and colleagues (8) excluded any trial that did not have a placebo control.

In their subgroup analysis, Amanatar and colleagues (8) analyzed their data by treatment duration. Trials of shorter durations (6 wk, 12 wk) showed a more favourable effect of testosterone. The longest trial included in their review (52 wk) showed a statistically

significant negative effect of testosterone replacement therapy (75); that is, participants in the testosterone group had significantly worse depression compared to those in the placebo group. The trial by Haren and colleagues (75) was not included in our review because it included men with testosterone levels in the range generally considered to be normal (> 12 nmol/L).

When we considered duration of treatment, we found that oral testosterone undecanoate and intramuscular testosterone enanthate were more effective than placebo for resolving symptoms of depression among trials with a treatment duration of at least 6 months. However, there were no differences in benefits among trials lasting less than 6 months. This is consistent with our hypothesis that the benefits of testosterone replacement therapy may take a period of time to become apparent.

In their subgroup analyses, Amanatkar and colleagues (8) reported a significant effect of testosterone replacement therapy on depressive symptoms among men aged less than 60 years (13 trials), and no significant effect among men aged older than 60 years (3 trials). Of note, Amanatkar and colleagues (8) used mean participant age to form their subgroups, while we took the standard deviation of the mean age into account in defining age groups (mean age ± 1 SD). In our study, we found no difference in depression among men aged less than 65 years who took testosterone replacement therapy, and we were unable to perform a network meta-analysis involving men aged 65 years and older because only 1 trial involved this population (19). Regardless of the definition of “older age” employed, Amanatkar and colleagues and our group both found limited data to support the effect of testosterone replacement therapy on depression among older men.

An earlier meta-analysis involving only patients with depression at baseline reported a significant effect of testosterone on depression (7). In their pairwise meta-analysis, Zarrouf and colleagues (7) included placebo-controlled randomized controlled trials involving men with major depressive disorder, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, and assessed using the Hamilton Rating Scale for Depression. In contrast, we included trials with a broad range of inclusion criteria. Only 2 trials in our analysis enrolled participants with depression at baseline (24, 32), while the remaining trials enrolled participants with AIDS wasting syndrome (30), erectile dysfunction (28), or older

men with symptoms of androgen deficiency (13, 14), or older age (19), or men who had been receiving testosterone replacement therapy for at least 3 months (31). Whether the participants also had at depression at baseline was not reported in most trials. For example, Hackett and colleagues (34) reported that 16% of patients in their trial had a past or current diagnosis of depression, but it is unknown what percentage was affected by depression at enrollment. Of the included trials, 4 allowed concomitant antidepressant use; the others did not allow or did not report antidepressant use. Of the 2 trials that enrolled participants with depression (24, 32), neither found a significant effect of testosterone on depressive symptoms.

Of the 12 trials included in our network meta-analysis, 4 reported a significant effect of testosterone replacement therapy on depression. Amory and colleagues (19), who enrolled men aged greater than 65 years with low testosterone, reported a significant effect of intramuscular testosterone enanthate (200 mg/2 wk) after 36 weeks of treatment; however, more participants in the testosterone group (6/21) than in the placebo group (2/18) were taking antidepressants during the treatment period. Kalinchenko and colleagues (29) reported a significant effect of intramuscular testosterone undecanoate (1000 mg/12 wk) among men aged 35–70 years with metabolic syndrome; patients with major depression treated with antidepressants were excluded from this trial. Zhang and colleagues found that oral testosterone undecanoate (120 or 160 mg/d depending on baseline testosterone level) had a positive effect on depression among men aged 50 years and older (13), while Cavallini and colleagues (14) reported a significant effect of oral testosterone undecanoate (160 mg/d) among men aged 60 years and older. Both Zhang and colleagues (13) and Cavallini and colleagues (14) enrolled participants with symptoms of androgen deficiency, which may include depressed mood; however, antidepressant use was not reported in either trial.

QUALITY OF LIFE

The effects of testosterone replacement products on quality of life have been evaluated in numerous primary studies, but this outcome had not been previously evaluated in a pooled analysis. In the current network meta-analysis, we found that 1 oral testosterone treatment significantly improved quality of life relative to placebo. Oral testosterone (dose based on baseline testosterone level, either 120 or 160 mg/d) significantly improved quality of life

relative to placebo; however, oral testosterone undecanoate at 160 mg/d did not. Only 1 trial involved this dosing strategy based on testosterone level at baseline (13); this trial was at overall high risk of bias. Zhang and colleagues (13) reported that participants with a baseline testosterone level between 8 and 12 nmol/L received 120 mg/d, while participants with baseline testosterone less than 8 nmol/L received 160 mg/d. The number of participants who received each dose was not reported, and this trial was judged to be at high risk of bias because of inadequate blinding. Further study is required to verify the findings of Zhang and colleagues (13).

In our subgroup analysis, we found that there was no difference between placebo and any of the routes of administration, or among the routes, in participants' quality of life. We also found no difference between placebo and any treatment or among the treatments for quality of life when the studies were grouped by duration of treatment or participant age.

ERECTILE FUNCTION

We found no effect of any testosterone replacement therapy on erectile function. This finding is consistent with that from our earlier network meta-analysis involving Health Canada–approved testosterone replacement products (74) and with the findings from a 2007 meta-analysis by Bolona and colleagues (9). In their meta-analysis, Bolona and colleagues (9) found no significant effect of testosterone replacement therapy on erectile function among men with low testosterone and sexual dysfunction (4 trials; SMD 0.80, 95% CI –0.10 to 1.60).

Our network meta-analysis of erectile function included 10 trials, including 5 different testosterone replacement products. We found no significant difference between placebo and any of the testosterone products or among the products for erectile function. Of the trials included in our analysis, 2 included men with sexual dysfunction at baseline (28, 41). The other trials used non-specific criteria for inclusion, such as “one or more symptoms of low T,” or with no criteria other than low testosterone levels. Three of the 10 included trials reported a significant difference in erectile function between placebo and testosterone-treated patients (14, 48, 54). The trial by Hackett and colleagues included participants with a low score on the Aging Males Symptoms (AMS) scale at baseline; the prevalence of erectile

dysfunction at baseline was 84% based on AMS score (< 25). Cavallini and colleagues (14) included participants with symptoms of androgen decline at baseline, while Chiang and colleagues (48) did not report whether such symptoms were present at baseline. The prevalence of erectile dysfunction at baseline was not reported in either trial. The trials by Cavallini and colleagues (14) and by Chiang and colleagues (48) were both judged to be at high risk of bias for incomplete reporting of efficacy data.

We found no difference in erectile function between the routes of administration. We also found no differences in erectile function among trials that involved a treatment duration of more or less than 6 months or aged less than 65 years. This finding is consistent with our main analysis that found no effect between any testosterone replacement therapy and placebo or among the treatments.

We identified 3 trials that assessed erectile function following testosterone treatment involving men aged less than 65 years (28, 29, 37), and no trials involving men aged 65 years and older. Among men aged less than 65 years, there were no significant differences between the testosterone replacement therapies and placebo or among the treatments; however, only 2 treatments were included in this network. In their 2007 pairwise meta-analysis, Bolona and colleagues (9) reported a significant increase in erectile function among men aged less than 60 years (SMD 1.80, 95% CI 1.00 to 2.70), and a non-significant effect among men aged more than 65 years. Of the 2 trials that they included in the less than 60 year group, we excluded both because of the treatment duration was less than 3 months. Both trials that Bolona and colleagues (9) included in the over 60 year group were included in our systematic review (14, 54); however, the mean participant age minus 1 SD was not more than 65 for either trial; as such, these studies were not included in our over 65-year subgroup.

LIBIDO

Our findings of no significant improvement in libido after testosterone replacement therapy are inconsistent with the findings by Bolona and colleagues (9), who found a positive effect of testosterone on libido among hypogonadal men with sexual dysfunction (any testosterone product v. placebo; 5 trials; SMD 1.31, 95% CI 0.40 to 2.22) (9). In contrast to Bolona and colleagues, we included only trials with a treatment duration of more than 3 months. Of the

10 primary trials included in our systematic review for this outcome, 3 trials reported a significant increase in libido relative to placebo (14, 34, 54). Hackett and colleagues (34) reported an improvement among men with type 2 diabetes and a low AMS score after treatment with intramuscular testosterone undecanoate (1000 mg/12 wk). Steidle and colleagues (54) reported a significant improvement in libido among men with symptoms of hypogonadism after treatment with 1% testosterone gel at 100 mg/d (but no effect at 50 mg/d); it should be noted, however, that this trial was judged to be at high risk of bias because of incomplete reporting of benefits data. Cavallini and colleagues (14) reported improved libido among men aged greater than 60 years with symptoms of “androgen decline” after treatment with oral testosterone undecanoate (160 mg/d); however, this trial was judged to be at unclear risk of bias for randomization, allocation concealment, blinding (subjective outcomes) and addressing incomplete data for benefits outcomes.

Of the 3 treatments that showed a significant effect in the primary studies, 2 (IM TU 1000 mg/12 wk, 1% gel 100 mg/d) were not significant in our network meta-analysis, which involved use of a random-effects model. However, all 3 were significant under the fixed-effects model. The credible intervals that result from random-effects models are generally considered to be more conservative than those from fixed-effects models, and random-effects models may be more appropriate if there is between-study heterogeneity, which is the case for this outcome (comparison of any testosterone product v. placebo had an I^2 value of 94%, which is considered very high).

We found no differences between the routes of administration for libido. In their 2007 meta-analysis, Bolona and colleagues (9) reported that oral testosterone was associated with a significant improvement in libido relative to placebo (SMD 1.60, 95% CI 0.87 to 2.34); however, the authors noted that there was high heterogeneity ($I^2 = 59\%$) across trials that involved oral preparations. Of the 5 trials included in this analysis by Bolona and colleagues (9), we excluded 3 from our systematic review because of the treatment duration was less than 3 months (76-78).

The effects of testosterone replacement therapy on libido may, in part, depend on treatment duration. We found no significant difference in libido between any testosterone replacement therapy and placebo or among the testosterone therapies in

trials with a treatment duration of 6 months or longer. However, among trials with a treatment duration of less than 6 months, we found that testosterone 1% gel was significantly better than placebo, patch (5 mg/), and oral testosterone undecanoate at 160 mg/d at improving libido. We also found that oral testosterone undecanoate at 120 mg/d was significantly better at improving libido compared with oral testosterone undecanoate at 160 mg/d.

To the best of our knowledge, this is the first pooled analysis showing a difference in efficacy of testosterone replacement therapy by duration of treatment. This difference in efficacy by treatment duration may partly explain the differences and high heterogeneity reported by Bolona and colleagues (9) in their pairwise meta-analysis.

3.4.3 INFLUENCE OF INDUSTRY FUNDING

When we analyzed data from only trials that reported having no industry funding, there were no significant differences between placebo and any of the included treatments or among the treatments for depression, quality of life, erectile function, or libido. These results were consistent with the primary analysis involving all trials for erectile function and libido. However, for depression and quality of life, treatments that were associated with a significant effect when all trials were included no longer showed a significant difference when only trials with no industry funding were considered. This may suggest that the funding source may be a source of bias in some trials of testosterone replacement therapies.

An influence of funding on the outcome of trials involving testosterone replacement therapies has been previously suggested. In a meta-analysis of cardiovascular-related outcomes among men taking a testosterone replacement product, Xu and colleagues (4) found a difference in effect size among trials reporting industry funding compared to those who did not. Trials that reported funding from a pharmaceutical source reported a lower odds of a cardiovascular-related event compared with the estimate from trials funded by pharmaceutical companies. To the best of our knowledge, this is the first analysis to examine the influence of funding on benefit outcomes for testosterone replacement therapy.

3.4.4 PUBLICATION BIAS

Publication bias was assessed by visually examining funnel plots for each outcome. In these analyses, we found potential publication bias for depression, with an absence of small trials showing a negative effect of testosterone replacement therapies. The funnel plot for quality of life was not suggestive of publication bias; however, we cannot conclusively rule it out. Although we had intended to assess publication bias for erectile function and libido, less than 10 studies were available for each outcome, which makes the assessment of publication bias unreliable. The funnel plots for erectile function and libido, based on 9 and 7, are both suggestive of publication bias; both are missing small trials with negative effects of studies respectively. However, there are other potential causes of asymmetry in the funnel plots (poor methodological design, inadequate analysis, heterogeneity, or chance); these cannot be ruled out in the present analyses (11).

3.4.5 INFLUENCE OF RISK OF BIAS

In order to assess the benefits of testosterone replacement therapy among trials at low risk of bias, we classified trials as being at low, unclear, or high risk based on their score for 3 domains of the Cochrane risk of bias tool (allocation concealment, blinding [subjective outcomes], incomplete data addressed [efficacy]). When we considered only trials that scored low risk for all 3 of these domains, we found no significant effect of testosterone replacement therapy relative to placebo, or among the therapies, for depression, erectile function, and libido. For quality of life, we found that testosterone patch (5 mg/d) was better than placebo, 1% testosterone gel (100 mg/d), and oral testosterone undecanoate (160 mg/d) when only trials at low risk of bias were included in the network.

The findings from our analysis of only trials at low risk of bias were consistent with the findings from primary analysis for erectile function and libido. However, there were differences between the analyses for depression and quality of life. In our primary analysis that included all trials, we found a significant improvement in depression for oral testosterone (T-based dose 120 or 160 mg/d, or 160 mg/d) and intramuscular testosterone enanthate (200 mg/2wk). When only trials at low risk of bias were considered, these

treatments were not included in the network, and there were no significant differences among the included treatments (1% testosterone gel 100 mg/d, IM TU 1000 mg/12 wk).

In the primary analysis, which included all trials that assessed quality of life, we found a significant improvement in quality of life associated with the use of oral testosterone undecanoate (T-based dose, 120 or 160 mg/d) relative to placebo; there were no significant differences among the treatments. When we considered only trials at low overall risk of bias, we found a significant improvement in quality of life with the use of testosterone patch (5 mg/d) relative to placebo. In the head-to-head comparisons, we found that testosterone patch (5 mg/d) was significantly better than 1% testosterone gel (100 mg/d) and oral testosterone undecanoate (160 mg/d). The difference in findings between the analysis that included all trials and the analysis that included only trials at low risk of bias suggests that trials at high or unclear risk of bias had an influence on our primary findings, and the results should be interpreted with caution. As well, because a large number of trials were assessed as being at high or unclear risk of bias, we were unable to include a number of treatments in our analysis. Additional high-quality trials are needed to more accurately assess the benefits of testosterone replacement therapy in this population.

3.4.6 STRENGTHS AND LIMITATIONS

We performed a comprehensive systematic review of the published and grey literature without language or date restrictions. We included only trials that enrolled men with hypogonadism (a mean total testosterone level < 12 nmol/L at baseline or whose inclusion criteria specified this cutoff). This is in keeping with the most recent clinical practice guidelines, which recommend that testosterone be offered only to men with unequivocally low serum testosterone levels (12).

Our study had some limitations that require consideration. First, the quality of the included trials was generally low based on our assessment of risk of bias, primarily because of unclear or inadequate reporting. In particular, allocation concealment and blinding were not well described, which may have had an impact on the reliability of subjective outcome data. Second, the duration of treatment may have been too short to see an effect of testosterone replacement therapy for all outcomes. Although total testosterone levels normalized within

the treatment period with most of the included treatments, it is possible that outcomes such as depression and quality of life may take longer to resolve. We included trials with a treatment duration of at least 3 months; however, the duration of most included trials was between 3 months and 1 year. This duration of treatment may not be sufficient to resolve symptoms.

Third, publication bias cannot be ruled out for most outcomes. The assessment of publication bias for libido and erectile function involved 9 and 7 trials, respectively, which is generally considered to be too few for proper assessment (11). The funnel plots for analysis of publication bias for depression and quality of life did not rule out the potential for publication bias for either outcome.

Fourth, the amount of data for some subgroups was limited, and network meta-analyses could not be performed for some subgroups because of a lack of data. As well, for some outcomes, trials had to be omitted from the network meta-analysis because they did not connect to the network through a common comparator.

3.4.7 CONCLUSION

We found that most testosterone replacement therapies increased total testosterone level. However, significant improvements in depression and quality of life were found for only a few of the investigated treatments, and we found no improvement in erectile function or libido. The effect of testosterone replacement therapy among men with low testosterone depended, in part, on the route of administration and duration of treatment; however, the effects varied by outcome. The quality of the included studies was generally unclear or poor, and caution should be used in interpreting the results. Additional high-quality studies are needed to evaluate the benefits of testosterone replacement therapy among hypogonadal men.

3.5 REFERENCES

1. Administration UAFDA. Joint meeting for bone, reproductive and urologic drugs advisory committee (BRUDAC) and the drug safety and risk management advisory committee (DSARM AC). 2014.
2. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med* 2013;173(15):1465-6.
3. Administration UFaD. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. 2015 [cited May 11, 2015]. Available: www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf.
4. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108.
5. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014;13(10):1327-51.
6. Fernandez-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, et al. Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010;95(6):2560-2575.
7. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract* 2009;15(4):289-305.
8. Amanatkar HR, Chibnall JT, Seo BW, Manepalli JN, Grossberg GT. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ann Clin Psychiatry* 2014;26(1):19-32.
9. Bolona ER, Uruga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82(1):20-8.
10. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JPA, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Arch Intern Med* 2015;162(11):777-84.
11. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons; 2008.
12. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-59.
13. Zhang XW, Liu ZH, Hu XW, Yuan YQ, Bai WJ, Wang XF, et al. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. *Chin Med J* 2012;125(21):3806-10.
14. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology*. 2004;63(4):641-6.
15. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 2: Generalised Linear Modelling Framework for Pairwise and Network

Meta-Analysis of Randomised Controlled Trials. Available:
www.nicesdu.org.uk/TSD6%20Software.final.08.05.12.pdf.

16. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, meta-regression, bias and bias-adjustment May 2011. Available: www.nicesdu.org.uk/TSD6%20Software.final.08.05.12.pdf.
17. Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Statistics Med* 2009;28(14):1861-81.
18. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS User Manual. Version 1.4.2003 Available: www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual114.pdf.
19. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab*. 2004;89(2):503-10.
20. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006;296(19):2351-61.
21. Behre HM, Tammela TL, Arver S, Tolra JR, Bonifacio V, Lamche M, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male*. 2012;15(4):198-207.
22. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009;54(10):919-27.
23. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(6):726-33.
24. Shores MM, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J Clin Psychiatry* 2009;70(7):1009-16.
25. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-22.
26. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, et al. The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). *Int J Clin Pract* 2014;68(2):203-15.
27. Stout M, Tew GA, Doll H, Zwierska I, Woodroffe N, Channer KS, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *Am Heart J* 2012;164(6):893-901.
28. Spitzer M, Basaria S, Travison TG, Davda MN, Paley A, Cohen B, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med* 2012;157(10):681-91.

29. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol* 2010;73(5):602-12.
30. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;129(1):18-26.
31. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999;84(10):3469-78.
32. Orenge CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. *J Geriatr Psychiatry Neurol* 2005;18(1):20-4.
33. Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20(4):378-87.
34. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med* 2013;10(6):1612-27.
35. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol.* 2004;172(2):658-63.
36. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care.* 2011;34(4):828-37.
37. Ho CC, Tong SF, Low WY, Ng CJ, Khoo EM, Lee VK, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU International.* 2012;110(2):260-5.
38. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc* 2010;58(6):1134-43.
39. Shigehara K, Sugimoto K, Konaka H, Iijima M, Fukushima M, Maeda Y, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. *Aging Male* 2011;14(1):53-8.
40. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95(2):639-50.
41. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. *Aging Male* 2009;12(4):104-12.

42. Merza Z, Blumsohn A, Mah PM, Meads DM, McKenna SP, Wylie K, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl* 2006;29(3):381-91.
43. Raynaud JP, Legros JJ, Rollet J, Auges M, Bunouf P, Sournac M, et al. Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every 2 days for 1 year to hypogonadal men. *J Steroid Biochem Mol Biol* 2008;109(1-2):168-76.
44. Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 1998;83(9):3155-62.
45. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res* 2009;21(2):129-38.
46. Hohl A, Marques MO, Coral MH, Walz R. Evaluation of late-onset hypogonadism (andropause) treatment using three different formulations of injectable testosterone. *Arq Bras Endocrinol Metabol* 2009;53(8):989-95.
47. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 2010;33(11):776-83.
48. Chiang HS, Cho SL, Lin YC, Hwang TI. Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection: evaluation by IIEF score. *Urology* 2009;73(4):762-6.
49. Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res* 2007;19(4):411-7.
50. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003;6(1):1-7.
51. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab* 2000;85(1):60-5.
52. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU International* 2003;91(1):69-74.
53. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-53.
54. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 2003;88(6):2673-81.
55. Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab* 2014;306(4):E433-E42.

56. Sheffield-Moore M, Dillon EL, Casperson SL, Gilkison CR, Paddon-Jones D, Durham WJ, et al. A randomized pilot study of monthly cycled testosterone replacement or continuous testosterone replacement versus placebo in older men. *J Clin Endocrinol Metab* 2011;96(11):E1831-E7.
57. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol* 2009;161(3):443-9.
58. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis* 2006;47(2):251-62.
59. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl* 1999;22(4):261-5.
60. Jockenhovel F, Blum WF, Vogel E, Englaro P, Muller-Wieland D, Reinwein D, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab* 1997;82(8):2510-3.
61. Jockenhovel F, Vogel E, Reinhardt W, Reinwein D. Effects of various modes of androgen substitution therapy on erythropoiesis. *Eur J Med Res* 1997;2(7):293-8.
62. Sih R, Morley JE, Kaiser FE, Perry HM, III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997;82(6):1661-7.
63. Kang SM, Jang Y, Kim JY, Chung N, Cho SY, Chae JS, et al. Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. *Am J Cardiol* 2002(7):862-4.
64. Kuhnert B, Byrne M, Simoni M, Kopcke W, Gerss J, Lemmnitz G, et al. Testosterone substitution with a new transdermal, hydroalcoholic gel applied to scrotal or non-scrotal skin: a multicentre trial. *Eur J Endocrinol* 2005;153(2):317-26.
65. Cavallini G, Biagiotti G, Lo GC. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 2012;33(3):381-8.
66. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ. Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab* 2003;88(1):358-62.
67. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011;8(7):2079-89.
68. Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;7(10):3495-503.
69. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 2008;11(3):140-5.
70. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008;68(7):641-8.
71. Schubert M, Minnemann T, Hubler D, Rouskova D, Christoph A, Oettel M, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab* 2004;89(11):5429-34.

72. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000;283(6):763-70.
73. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male* 2003;6(1):13-7.
74. G.A. Wells JE, S. Kelly, J. Peterson, A. Johnston, A. Kotb, L. Chen, B. Skidmore. Testosterone in the treatment of androgen deficiency. November 17, 2014. Available: <http://odprn.ca/drug-class-review/completed-reviews/testosterone-replacement-therapy/>
75. Haren MT, Wittert GA, Chapman IM, Coates P, Morley JE. Effect of oral testosterone undecanoate on visuospatial cognition, mood and quality of life in elderly men with low-normal gonadal status. *Maturitas* 2005;50(2):124-33.
76. Carani C, Zini D, Baldini A, Della Casa L, Ghizzani A, Marrama P. Effects of androgen treatment in impotent men with normal and low levels of free testosterone. *Arch Sex Behav* 1990;19(3):223-34.
77. Bancroft J, Wu FC. Changes in erectile responsiveness during androgen replacement therapy. *Arch Sex Behav* 1983;12(1):59-66.
78. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol* 1981;14(1):49-61.
79. Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.

CHAPTER 4: HARMS ASSOCIATED WITH THE USE OF TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL MEN

4.1 INTRODUCTION

Testosterone replacement therapy is marketed as a fix-all for old age and has been prescribed at an increasing rate among men (1, 2) despite concerns about its safety. Based on the early stoppage of a randomized controlled trial (RCT) and the results of 2 cohort studies, the US Food and Drug administration and Health Canada both issued warnings in 2014 about an increased risk of cardiovascular events among testosterone users. In 2010, the Testosterone in Older Men with Mobility Limitations (TOM) trial was terminated by its data safety and monitoring board after interim analyses of adverse events showed significantly more adverse cardiovascular events in the testosterone group than in the placebo group (3). The retrospective cohort study by Vigen and colleagues (4) involving men with low testosterone who had undergone coronary angiography found an increased absolute risk of a cardiovascular event among men taking a testosterone replacement therapy relative to men not taking testosterone (absolute risk difference 5.8%, 95% confidence interval [CI] -1.4% to 13.1%). Similarly, Finkle and colleagues (5) reported an increased risk of myocardial infarction among men taking a testosterone product compared to those taking a phosphodiesterase type 5 inhibitor; however, the baseline testosterone levels were not available in this study.

Although the harms associated with testosterone replacement therapy have been assessed by meta-analyses, the results have been contradictory. Corona and colleagues (6) reported no increased risk of cardiovascular death, myocardial infarction, stroke or a composite of non-fatal myocardial infarction, cardiovascular death, myocardial infarction, cardiovascular death, stroke, acute coronary syndrome and heart failure. In contrast, Xu and colleagues (7) reported a significantly increased risk of cardiovascular-related events (composite: cardiac disorder, cardiovascular complaints, cardiovascular events, vascular disorders). Both reviews included trials that enrolled both hypogonadal and eugonadal men, although Corona and colleagues (6) reported no increased risk of cardiovascular events among hypogonadal men

in a subgroup analysis. Xu and colleagues (7) included trials of 3 months' duration and longer, while Corona and colleagues (6) imposed no restriction on trial length.

Concern about an increased risk of prostate cancer among men taking testosterone replacement therapy dates back to the 1940s (8), and current guidelines recommend against starting testosterone replacement therapy in patients with prostate cancer or elevated PSA (9). The results of previous meta-analyses have been contradictory: a 2005 meta-analysis reported an increase in a composite of prostate-related events among men taking testosterone replacement therapy (10), while a 2013 meta-analysis found no significant difference in the incidence of prostate cancer (11). A 2014 meta-analysis involving 22 randomized controlled trials of up to 36 months duration investigated the odds of prostate cancer among men with hypogonadism (12). The authors reported no increased risk of prostate cancer among men taking a testosterone replacement therapy; this was consistent in studies with a treatment duration of more or less than 1 year (12), and did not differ by route of administration. Whether the risk of prostate cancer differs by type of testosterone replacement therapy has not been investigated.

Because of the controversy surrounding the harms associated with testosterone replacement therapy, we sought to summarize the currently available evidence from randomized controlled trials and non-randomized studies. In contrast with previous systematic reviews, we included only studies involving hypogonadal men to provide an estimate of adverse events in this population. We performed a systematic review and network meta-analysis of testosterone replacement therapies in adult men with low testosterone.

4.2 METHODS

This review of harms was performed as part of the efficacy review in Chapter 3. The methods are described in detail in Chapter 3 and are summarized here. Of note, non-randomized studies of interventions (hereafter referred to as "non-randomized studies") were eligible for inclusion in the review of harms (Chapter 4), but not in the review of efficacy (Chapter 3).

This systematic review followed the network meta-analysis extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (13) and the Cochrane Handbook for Systematic Reviews of Interventions (14). The protocol was registered before study selection was initiated (PROSPERO no.: CRD42014009963).

4.2.1 SEARCH STRATEGY

Electronic search strategies (Appendix 1) were developed by an experienced medical information specialist. Using the OVID platform, we searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase Classic+Embase on June 8, 2014. We also searched CENTRAL in the Cochrane Library on Wiley on the same date. Strategies used a combination of controlled vocabulary and keywords and were adjusted across the databases. We used research filters to identify randomized, non-randomized and controlled clinical trials, as well as non-randomized observational studies. A grey literature search of relevant databases and web sites was performed using resources listed in CADTH's *Grey Matters Light*.

4.2.2 STUDY SELECTION

We included randomized controlled trials involving men aged 18 years and older with androgen deficiency (serum total testosterone ≤ 12 nmol/L or free testosterone < 225 pmol/L). All testosterone replacement products were eligible for inclusion. Studies involving testosterone precursors (e.g., dehydroepiandrosterone [DHEA]) or that artificially suppressed endogenous testosterone levels were excluded. The comparator could be a placebo, different testosterone product, or the same testosterone product at a different dose. Studies were not excluded based on outcome. We excluded trials with fewer than 10 participants or less than 12 weeks' duration. Cross-over trials were eligible for inclusion; data were only included in the analysis if the first period data were reported for each treatment group and if the duration of initial treatment was 12 weeks or longer. Non-randomized studies were eligible for inclusion if they had an appropriate comparison group (e.g., untreated hypogonadal men); studies that used eugonadal men as a comparison group were excluded.

Eligibility criteria were applied to each title and abstract identified in the literature search by 2 independent reviewers (J.E., J.P.) in a standardized manner. Any trial that was considered

to be relevant by 1 reviewer was obtained in full-text format. The full-text version of each potentially relevant article was independently assessed by 2 reviewers (J.E., J.P., A.J.), and a final decision made for inclusion. Any uncertainties were resolved by discussion and consensus with a third review author (S.K.). Reviewers were not blinded to study authors or centre of publication prior to study selection.

4.2.3 DATA EXTRACTION AND QUALITY ASSESSMENT

One reviewer extracted data from selected trials, and a second reviewer checked the data for accuracy (J.E., J.P., A.J., A.K.). Study and participant characteristics, as well as data for *a priori* defined adverse events, were extracted using standardized data abstraction forms in DistillerSR. The original, primary publication for each unique trial was included. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias for RCTs; we used SIGN50 for cohort studies to assess bias for non-randomized studies. Withdrawals due to adverse events were classified as a subjective outcome; all other harm outcomes were considered to be objective.

4.2.4 OUTCOMES

The outcomes of interest were cardiovascular death, myocardial infarction, stroke, newly diagnosed disease (prostate cancer, cardiovascular disease, diabetes), erythrocytosis, withdrawals due to adverse events, and serious adverse events. If a participant died of a myocardial infarction, they were counted once for the outcome "myocardial infarction" and once for the outcome "cardiovascular death." Cardiovascular death could include sudden cardiac death, death due to myocardial infarction, heart failure, stroke, or cardiovascular hemorrhage, or death due to a cardiovascular procedure. Serious adverse events and erythrocytosis were extracted as described by the study authors (e.g., no inferences made as to the seriousness of an event or based on hemoglobin levels). We inferred that no cardiovascular deaths had occurred in a trial if the number of participants who completed the trial was equal to the number randomized or if the authors stated that no serious adverse events had occurred. We inferred that no withdrawals due to adverse events occurred if all participants completed the trial.

4.2.5 PUBLICATION BIAS

Funnel plots were used to assess potential publication bias for each outcome. The standard error (SE) for each estimate was plotted (vertical axis) against the odds ratio (horizontal axis). The pooled estimate is plotted as a vertical dashed line.

4.2.6 STATISTICAL ANALYSIS

META-ANALYSIS

Pairwise random-effects meta-analyses were conducted by comparing any testosterone replacement treatment with placebo, and by comparing route of administration (oral, intramuscular injection [IM], topical) with placebo. For trials that involved 2 or more testosterone replacement therapies compared with placebo, the data for all testosterone replacement therapy arms were pooled before analysis. Heterogeneity was evaluated by examining the forest plots and inconsistency index (I^2). Peto odds ratios were used for rare events; random-effects models were used for non-rare events. Results having a p value of less than 0.05 and a 95% confidence interval (CI) excluding 1.0 were considered to be statistically significant. Meta-analyses were conducted using Comprehensive Meta-Analysis and Review Manager of the Cochrane Collaboration.

NETWORK META-ANALYSIS

Bayesian network meta-analyses were performed for the following outcomes: cardiovascular death, myocardial infarction, prostate cancer, serious adverse events, and withdrawals due to adverse events. There were insufficient data to perform network meta-analyses for the other harms outcomes. The nodes for network meta-analyses were decided in consultation with clinical experts and were based on the belief that the products each had potentially different efficacy and safety profiles. The frequency data from each trial were incorporated in the network using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK), using a binomial likelihood model which allows for the use of multi-arm trials (15, 16). Placebo was chosen as the reference group (index node) in the model. Both fixed- and random-effects network meta-analyses were conducted; assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) and comparison of residual deviance to the number of unconstrained data points (15, 17). Point estimates and 95%

credible intervals were derived using Markov Chain Monte Carlo methods. Vague priors were assigned for basic parameters throughout (15) and informative priors were considered for the variance parameter were based on Turner and colleagues (18). To ensure model convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed (19). Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations (19, 20). Following the base-case analyses involving all trials for each outcome, 2 additional analyses were performed where necessary. In the first, an adjusted continuity correction was applied to each cell with a zero event count (21). In the second, any treatments for which there were zero events recorded were removed from the network, to allow more precise assessment of odds ratios and credible intervals for the harms associated with testosterone replacement therapies that had reported events. Odds ratios with 95% credible intervals are reported in the following sections; relative risks and risk differences are presented in Appendix 8.

4.2.7 SENSITIVITY ANALYSIS

- a) Influence of the funding source:* A recent meta-analysis of cardiovascular-related events among men taking testosterone replacement therapy reported that the odds of an event was higher in trials not funded by a pharmaceutical company than in those funded by a pharmaceutical company (4). Whether this apparent influence of the funding source extends to benefit outcomes is unknown. In this analysis, we included only data from trials that reporting having no industry funding. Trials that reported a mixture of industry and non-industry funding were excluded from this analysis, as were trials that did not report the funding source. Data were analyzed using the random-effects model, unless otherwise stated.
- b) Influence of bias:* In this analysis, we included only trials that we judged to be at low risk of bias, based on adequate allocation concealment, adequate blinding for subjective outcomes, and adequate consideration of incomplete data (completion over 80% and approximately equal in all arms). Data were analyzed using the random-effects model, unless otherwise stated. Withdrawals due to adverse events were considered to be subjective outcomes; all other safety outcomes were considered to be objective.

4.2.8 SUBGROUP ANALYSIS

Subgroups were selected a priori in consultation with clinical experts to compare the benefits of testosterone replacement therapy across variants in the population for which a plausible difference may exist. The subgroups specified a priori were age ($< v. \geq 65$ yr), duration ($< v. \geq 6$ mo treatment), route of administration, and comorbidities (diabetes, depression, hypertension, obesity, coronary artery disease, hyperlipidemia). We classified trials as involving patients aged less than 65 years if the mean age plus 1 standard deviation (SD) was below 65. We classified trials as involving patients aged 65 years or older if the mean age minus 1 SD was 65 or above.

4.3 RESULTS

4.3.1 CHARACTERISTICS OF THE INCLUDED STUDIES

After full-text screening, a total of 102 RCTs (70 unique trials) and 40 non-randomized studies (38 unique studies) met the inclusion criteria (Figure 1). Included and excluded records are listed in Appendices 2–4. Of the included RCTs, 7 were cross-over trials that did not report first-period data separately. Six trials reported no outcomes of interest, and 1 reported data in a non-useable form. The included randomized controlled trials were published between 1997 and 2014, with a treatment duration between 3 and 36 months. The included populations were heterogeneous, with a broad range of included populations (e.g., symptoms of androgen deficiency, chronic heart failure, diabetes, depression, obesity, limited mobility or frailty). The characteristics of the included randomized controlled trials are described more fully in Chapter 3.

Of the 38 included unique non-randomized studies (Appendix 7), 12 reported a safety outcome of interest (5 retrospective cohort studies, 7 prospective cohort studies). The included non-randomized studies were published between 1997 and 2014. The duration of the retrospective cohort studies was between 3 months and 2 years, while the duration of the prospective cohort studies was between 24 weeks and 2 years. One study was published in Russian (22); the remainder were published in English. The characteristics of the included studies that reported at least 1 outcome of interest are reported in Table 4.1.

FIGURE 4.1: SELECTION OF STUDIES FOR INCLUSION IN THE SYSTEMATIC REVIEW (PRISMA)

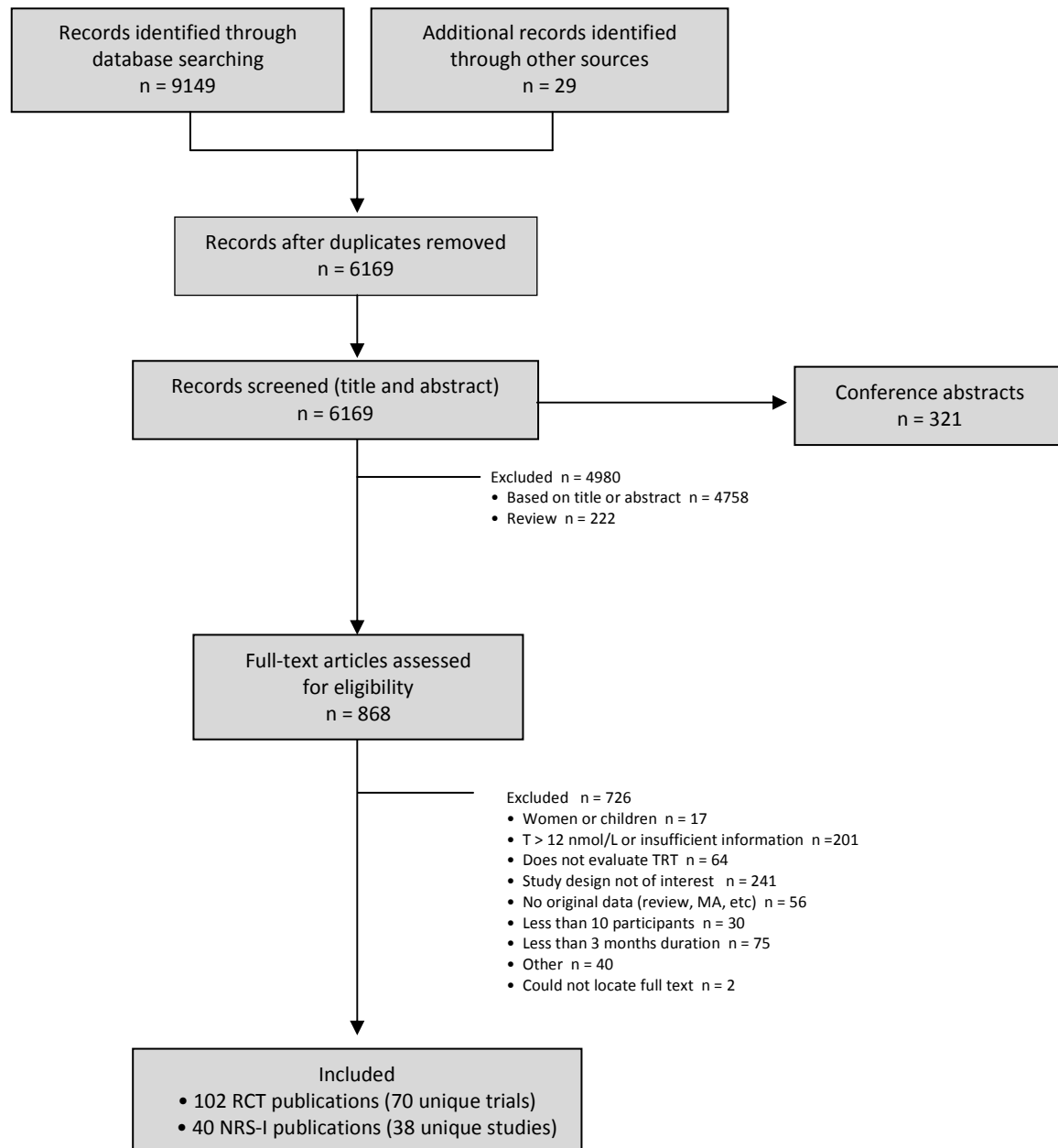


TABLE 4.1: CHARACTERISTICS OF INCLUDED NON-RANDOMIZED INTERVENTIONAL STUDIES

Study	Population	Duration	Group (no. in group)	Age, yr mean (SD)	Baseline total T, mean (SD), nmol/L [†]	Industry funding	Comment
Retrospective cohort							
Aydogdu 2013, p. 243	IHH	24 wk	Sustanon, IM 250 mg/3wk (28) Testogel 1%, gel, 50 mg/d (24) hCG, 5000 IU, 2x/ wk (25)	20.9 (1.4) 21.3 (1.6)	0.9 (0.6) 1.4 (1.3) 1.3 (1.8)	No	hCG group not eligible for inclusion. The definition of IHH involves sexual retardation, failure to undergo puberty, and low testosterone, LH and FSH, among other criteria
Vigen 2013, p. 1829	Men who underwent coronary angiography at a VA medical centre	Mean follow-up: 840 d	TRT, dose NR (1223) No treatment (7486)	60.6 (7.6) 63.8 (9.0 yr)	6.1 (2.2) 7.2 (2.6)	NR	Patients were categorized as initiating TRT if they filled a prescription for a patch, gel or injectable following coronary angiography based on pharmacy-dispensing data and were assumed to have continued treatment until an event occurred or end of follow-up
Shores 2012, p. 2050	> 40 yr treated at a VA medical center	20.2 (16.7) mo	TRT, dose NR (398) No treatment (633)	62.1 (10.6)	5.6 (2.2) 6.7 (1.9)	No	Non-industry funding reported for this study; 1 author has received research support from Abbott (Androgel), GSK (Testim), and BHR Pharmaceuticals (Androgel)
Rhoden 2006, p. 201	Hypogonadal men with negative prostate biopsy prior to initiation of TRT	12 mo	IM TRT, dose NR (33) Testim or Androgel 1%, dose NR (25)	58.3	10.3 (5.4) 10.2 (3.1)	No	Dose and percentage of gel NR
Guay 2000, p. 132	Men with ED and primary or secondary hypogonadism	2-3 months	IM TE, 200-300 mg/2-3 wk (25) Patch, 5 mg/d (16) Clomiphene citrate, oral, 3x/week (49)	40-80	Free T: 8.1-9.7 pg/ml	NR	Clomiphene citrate arm is not eligible for inclusion
Hajjar 1997, p. 3793	Elderly men	24 mo	IM TE or TC, IM 200 mg/2 wk (45) No treatment (27)	71.8 (SE 1.7) 69.9 (SE 1.9)	10.8 (4.7) 9.6 (3.8)	NR	
Prospective cohort							
Francomano 2014, p. 401	Severely obese men (mean BMI 42) with ≥ symptoms of hypogonadism	54 wk	DPE (12) DPE + Nebido, IM 1000 mg/12 wk (12)	53 (8) 56 (9)	8.2 (1.8) 8.5 (1.8)	NR	33% and 40% in the DPE and DPE+T groups, respectively, had ED at baseline; treatment period was followed by a 24-wk observation period
Blick 2013, p. 30	HIV/AIDS	12 mo	Androgel 1%, gel, 50 mg/d (92) Testim 1%, gel, 50 mg/d (75)	49.5 (8.1)	13.9 (5.5) 13.7 (7.2)	Yes	Inclusion criteria was total T < 12 nmol/l or free T < 50 pg/ml ; funded by Auxilium Pharmaceuticals, makers of Testim
Aversa 2012, p. 96	Middle-aged men with LOH and MetS	36 mo	Nebido, IM 1000 mg/12 wk (40) No treatment (20)	58 (10) 57 (8)	8.3 (2.4)	NR	Patients were previously enrolled in an RCT by the same group with the same drugs. Funding not reported; however, 1 author is a consultant for Eli-Lilly (not a manufacture of the study drug but does manufacture another testosterone product)
Morgunov 2011 (Russian)	T2DM, acquired androgen deficiency, and first episode of ischemic stroke	2 yr	No treatment (30) IM TU 1000 mg/12 wk (42)	61.4 (4.1)	9.3 (1.6) 9.2 (1.4)	NR	Patients had previously experienced a stroke
Dean 2005, p. 87	Aged 21-81 yr	Up to 12 mo	Testim 1%, 50 mg/d (NR) Testim 1%, 100 mg/d (NR)	58.5 (10.0)	8.1 (2.1)	NR	Number of participants per group was not reported. Funding was not reported, but study drug was provided by manufacturer
Wang 2004,	Aged 19-68 yr	36 mo	Androgel 1%, gel, 50 mg/d (NR)	51.5 (0.9)	14.1 (1.3)	No	This study was completed after an initial 6 month randomized

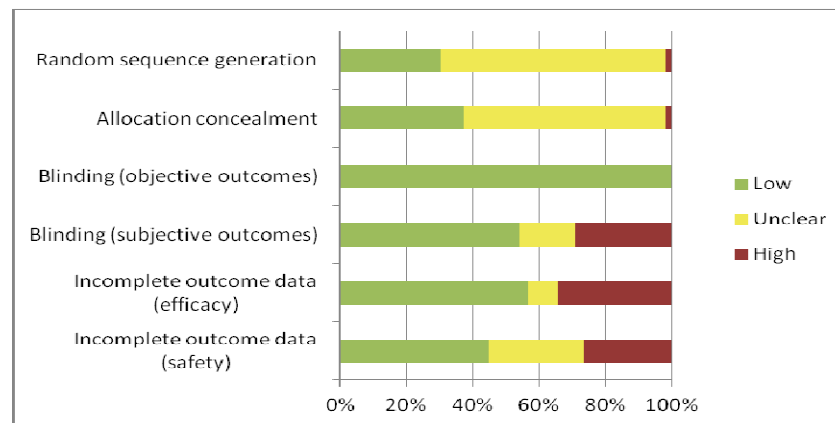
Study	Population	Duration	Group (no. in group)	Age, yr mean (SD)	Baseline total T, mean (SD), nmol/L [†]	Industry funding	Comment
p. 2085 (Swerdloff 2003 p.207)			AndroGel 1%, gel, 75 mg/d (NR) AndroGel 1%, gel, 100 mg/d (NR)		22.4 (2.7) 25.6 (2.4)		study for an additional 36 months; participants had a total of 42 months of gel exposure. Funding was by NIH grant, but study drug was provided by manufacturer
Note: DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NIH = National Institutes of Health, NR = not reported, RCT = randomized controlled trial, T = testosterone, T2DM = type II diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, VA = Veterans Affairs. *Characteristics presented for non-randomized studies that reported at least 1 outcome of interest. Data were not extracted from studies that reported no outcomes of interest: Kacker 2014, Trabado 2014, Muraleedharan 2013, Strollo 2013, McCullough 2012, Arafa 2012, Vignera 2011, Trabado 2011, Host 2010, Taylor 2010, Andrade 2009, Yaron 2009, Ross 2009, Thomson 2009, Gooren 2008, Vignera 2008, Kalinchenko 2008, Saad 2008, Agarwal 2005, Black 2004, Zitzmann 2003, Park 2003, Jin 2001, van den Bergh 2001, Kubler. †Unless otherwise stated.							

4.3.2 RISK OF BIAS

RANDOMIZED CONTROLLED TRIALS

The risk of bias for included RCTs was summarized in Chapter 3. In general, most trials were of low or unclear quality for the domains assessed. The overall risk of bias was unclear or high for most trials, primarily because of a lack of transparency in the reporting. In many trials, the method of randomization, allocation concealment, and blinding were not reported. Incomplete outcome data for harms outcomes was judged to be at unclear or high risk of bias for over 50% of the included trials.

FIGURE 4.2: RISK OF BIAS SUMMARY FOR INCLUDED RANDOMIZED CONTROLLED TRIALS THAT REPORTED AT LEAST 1 OUTCOME OF INTEREST



NON-RANDOMIZED INTERVENTIONAL STUDIES

We used SIGN50 to assess the quality of the included non-randomized studies of interventions (Table 4.2). The quality of the study published by Morgunov and colleagues (22) was not assessed because, although they reported 1 outcome of interest (stroke), we deemed this data to be ineligible for inclusion in our review. Morgunov and colleagues (22) assessed the incidence of stroke among men taking testosterone replacement therapy who had previously experienced a stroke (secondary stroke); in contrast, the other included studies assessed the first incidence of stroke.

Among the 11 studies for which quality was assessed, 5 were prospective cohort studies and 6 were retrospective cohort studies. Of the 5 prospective cohort studies, only 1 was given a

rating of acceptable (23). The reasons for receiving an unacceptable rating included study groups that differed in an important way (e.g., comprised of men with contraindications to testosterone replacement therapy) and poor reporting of the number of men assigned to each group.

Among the retrospective cohort studies, 2 received a rating of unacceptable (24, 25), primarily because of incomplete reporting of safety data (safety data not reported by treatment assignment, safety data provided only for a subset of patients).

TABLE 4.2: SIGN50 ASSESSMENT OF NON-RANDOMIZED STUDIES

Study*	Overall assessment of the study†	Comments
Francomano 2014	Unacceptable (–)	Prospective cohort. Obese men with low testosterone. Baseline characteristics were well matched on reported characteristics, but control group had contraindications to TRT, making them potentially different. 33% dropout in treatment group, zero in control group; no comparison between those who dropped out or who remained in study. SAE not defined as an outcome, but other outcomes defined.
Aydogdu 2013	Acceptable (+)	Retrospective cohort. Men with IHH (not late-onset hypogonadism). Group treated with hCG not eligible for inclusion in current review. SAE not defined as an outcome but reported that no SAEs were detected for any treatment group. Results are likely applicable to men with IHH but not LOH.
Blick 2013	Acceptable (+)	Prospective cohort. Groups were generally well matched on baseline characteristics with no statistically significant differences (except for study site). Patients in the 2 treatment groups were not followed for an equal length of time (Androgel: mean 6.1 yr; Testim: mean 1.9 yr). Skin reactions were assessed but not reported. Outcome assessment was not blinded to exposure status.
Vigen 2013	Acceptable (+)	Retrospective cohort. All-cause mortality was assessed via the Veterans Affairs vital status file (high sensitivity and agreement with the National Death Index). Myocardial infarction and ischemic stroke were assessed via <i>International Classification of Diseases, Ninth Revision</i> from Veterans Affairs inpatient treatment files. Conclusions based on a composite outcome. Sufficient data not reported to allow analysis of stroke or MI separately at each time point. Outcome assessment was not blinded to exposure status.
Aversa 2012	Unacceptable (–)	Prospective cohort. Men with multiple sclerosis and as late onset hypogonadism were included. Baseline characteristics were well matched but the control group was comprised of men who had refused or had contraindications to testosterone therapy. Adherence to treatment over 3 years was only 50% in the TU group. Those discontinuing TU but remaining in study for follow up were not included in the efficacy analysis. No definition was provided for serious adverse events.
Shores 2012	Acceptable (+)	Retrospective cohort. Hazard ratio for mortality takes person-years of observation into account. Adjusted HR and CIs provided (adjusted for age, site, hospitalization in the past year, diabetes, coronary artery disease). Outcome assessment was not blinded to exposure status. Exposure was determined via Veterans Affairs pharmacy records and outcomes were ascertained from 2 mortality databases.
Rhoden 2006	Acceptable (+)	Retrospective cohort. Patients had to have negative prostate biopsy before initiation of TRT, thus excluding any men with pre-existing large volume disease from the analysis. Type and dose of intramuscular testosterone not reported. Dose of Androgel and Testim not reported (data not provided separately by type). Outcome assessment was not blinded to exposure status.
Dean 2005	Unacceptable (–)	Prospective cohort. Poor reporting of the number of patients in each group and which group the safety events occurred in. The number of and reasons for withdrawals were not reported. Safety data were reported for overall but not by treatment group. Outcome assessment was not blinded to exposure status.

Study*	Overall assessment of the study†	Comments
Wang 2004	Unacceptable (–)	Prospective cohort (open-label extension of an RCT). The number of men assigned to each group was not reported. Safety data were poorly reported: 3 cases of prostate cancer reported but data could not be used in our analysis because the number of people in each group was not reported. Outcome assessment was not blinded to exposure status.
Guay 2000	Unacceptable (–)	Retrospective cohort. Safety data not reported by treatment group. Outcome assessment was not blinded to exposure status.
Hajjar 1997	Unacceptable (–)	Retrospective cohort. Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted. Outcome assessment was not blinded to exposure status.

Note: CI = confidence interval, hCG = human chorionic gonadotropin, IHH = idiopathic hypogonadotropic hypogonadism, HR = hazard ratio, MI = myocardial infarction, RCT = randomized controlled trial, SAE = serious adverse events, TRT = testosterone replacement therapy, TU = testosterone undecanoate.

*Non-randomized studies that reported at least 1 outcome of interest.

†Assessed by use of SIGN50 for cohort studies.

4.3.4 EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

Of the 10 harm outcomes of interest, there were sufficient data to perform network meta-analyses for 5 outcomes (Table 4.3). In each of the following sections, the results of meta-analysis (any testosterone product v. placebo) are described, followed by the results of network meta-analysis, where appropriate. The summary of the network characteristics is provided in Table 4.4. Outcomes for which insufficient data for meta-analysis were located are summarized narratively. The odds ratios, relative risk, and risk difference for each comparison is presented in Appendix 8, and a comparison of odds ratios under the random- and fixed-effects models is presented in Appendix 9.

TABLE 4.3: SUMMARY OF OUTCOMES BY ANALYSIS METHOD

Network meta-analysis	Meta-analysis	Narrative summary
Cardiovascular death	Stroke	Erythrocytosis
Myocardial infarction		Heart disease
Prostate cancer		Diabetes
Serious adverse events		Skin reactions
Withdrawals due to adverse events		

TABLE 4.4: SUMMARY OF NETWORK CHARACTERISTICS

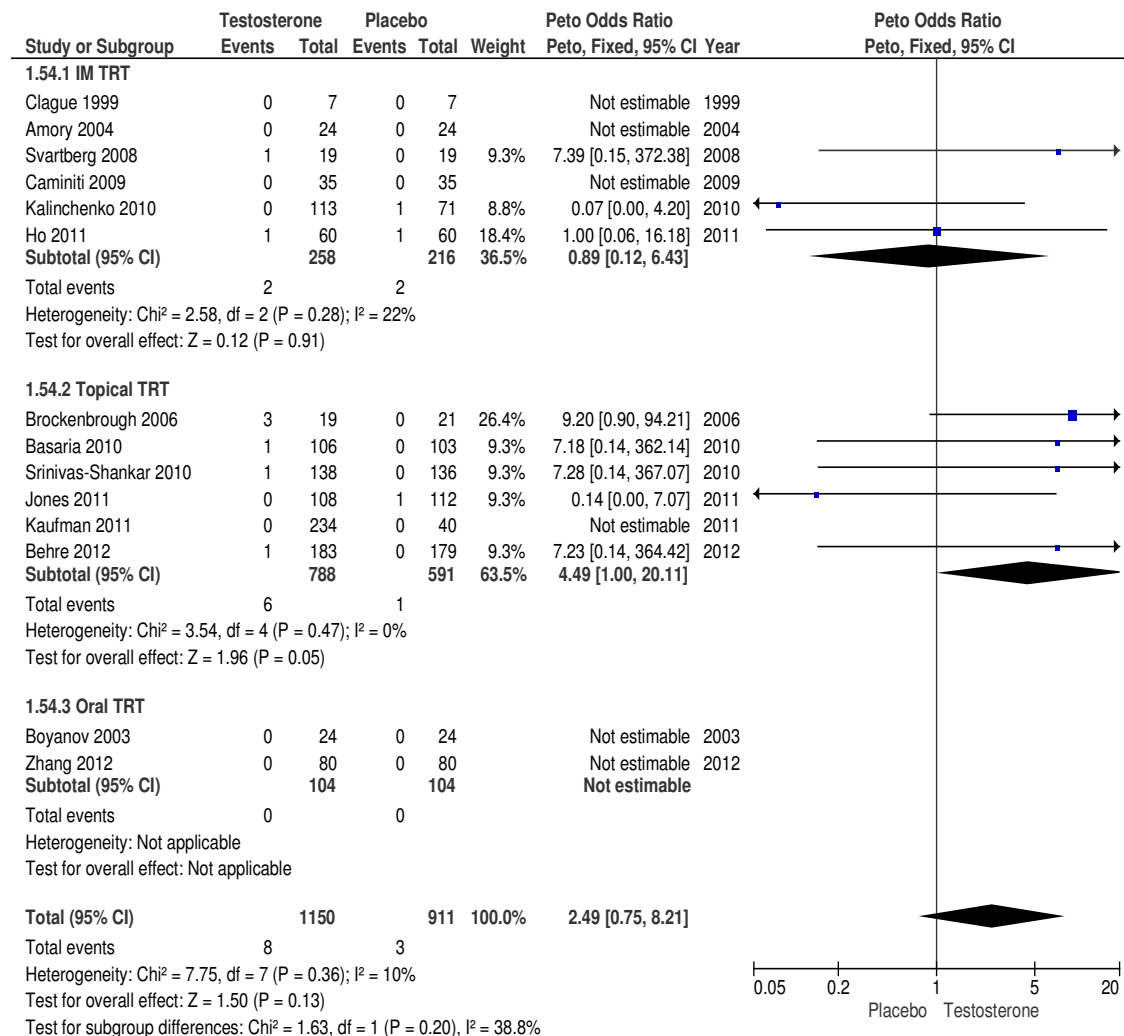
Characteristic	Cardiovascular death	Myocardial infarction	Prostate cancer	Serious AEs	Withdrawals due to AEs
No. of trials	15	10	11	13	70
No. of treatment nodes	9	8	9	9	21
No. of participants	2101	1562	2028	2184	3834
No. of comparisons	15	12	16	15	42
No. of 2-arm trials	15	9	10	12	39
No. of multi-arm trials	0	1	1	1	1
Note: AE = adverse event					

CARDIOVASCULAR DEATH

In total, 15 trials reported cardiovascular death during the treatment period (3, 26-39). Of these, 14 involved comparison with a placebo group. When all testosterone products were compared to placebo in a pairwise meta-analysis, there was no increased risk of cardiovascular death (OR 2.49, 95% CI 0.75 to 8.21; $I^2 = 10\%$) (Figure 3); however, there appeared to be an increased risk associated with the use of topical testosterone treatments (OR 4.49, 95% CI 1.00–20.11; $I^2 = 0\%$), with no difference in risk between placebo and oral or intramuscular forms. The finding of an increased OR associated with the use of topical testosterone is based on few studies and should be interpreted with caution.

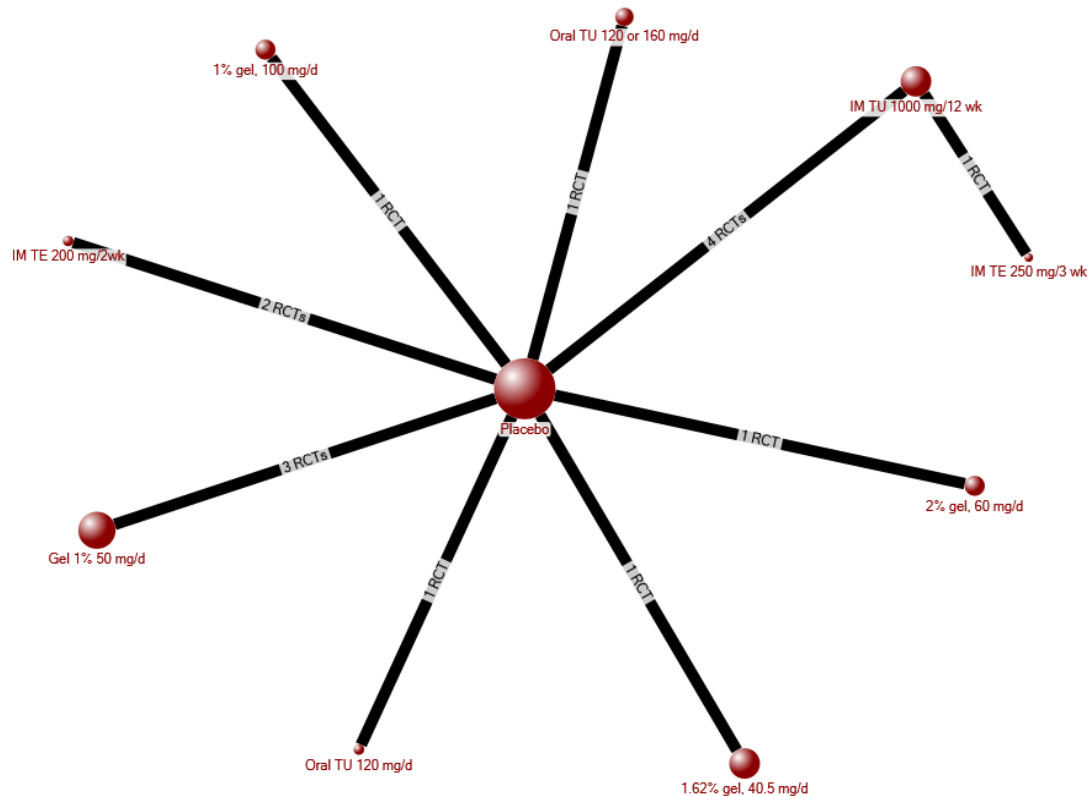
We next preformed network meta-analysis to compare the odds of cardiovascular death among the different testosterone products. Of the 70 RCTs included in the systematic review, 11 reported cardiovascular death as an adverse event (3, 26, 29-35, 38, 40). We were able to infer that no cardiovascular deaths had occurred during the treatment period for an additional 4 trials because of complete reporting (e.g., all participants completed the trial) (27, 36, 37, 39). The network for cardiovascular death included 2101 participants, and 9 treatments (Figure 4). Fifteen comparisons were made, based on 15 trials, each with 2 arms.

FIGURE 4.3: ODDS RATIO OF CARDIOVASCULAR DEATH AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY



The initial network included all treatments, with no continuity correction applied. This resulted in wide credible intervals for some comparisons, particularly those involving treatments with few participants and with zero event counts (Table 4.5). There was no significant difference in the odds of cardiovascular death between any of the treatments and placebo, or among the treatments (Table 4.5).

FIGURE 4.4: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH



In a subsequent analysis, an adjusted continuity correction was applied to all cells with a zero event count (21). The network comprised the same number of participants, treatments and comparisons as for the base case (Figure 4.4). The application of an adjusted continuity correction to cells with zero event counts resulted in narrower credible intervals. However, wide credible intervals were still obtained for some comparisons (Table 4.6), for example, comparisons involving intramuscular testosterone enanthate (250 mg/3 wk), which connected to the network through intramuscular testosterone undecanoate (1000 mg/12 wk) and included few participants ($n = 20$).

When treatments that had zero reported cardiovascular deaths were removed from the network (Table 4.7), the revised network included only 3 testosterone replacement therapies: 2 topical preparations and 1 intramuscular preparation. Compared with placebo, there was no significant difference in the odds of cardiovascular death associated with any of these treatments, and there was no difference between the treatments.

TABLE 4.5: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 120 or 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/3 wk
Gel 1%, 50 mg/d	3.54 (0.67, 23.88)	—								
Gel 1%, 100 mg/d	1.66 (0.05, 46.10)	0.48 (0.01, 18.20)	—							
Gel 1.62%, 40 mg/d	0.09 (0.00, 6.18)	0.02 (0.00, 2.11)	0.05 (0.00, 12.34)	—						
Gel 2%, 60 mg/d	0.10 (0.00, 3.45)	0.03 (0.00, 1.57)	0.06 (0.00, 10.53)	1.12 (0.00, 401.30)	—					
Oral TU 120 mg/d	0.24 (0.00, 18.95)	0.06 (0.00, 6.72)	0.14 (0.00, 43.77)	2.61 (0.00, 1684.00)	2.47 (0.00, 1683.00)	—				
Oral TU 120 or 160 mg/d	0.22 (0.00, 13.93)	0.06 (0.00, 5.48)	0.13 (0.00, 27.64)	2.56 (0.00, 1471.00)	2.43 (0.01, 1283.00)	0.93 (0.00, 663.40)	—			
IM TU, 1000 mg/12 wk	0.53 (0.08, 2.74)	0.14 (0.01, 1.67)	0.32 (0.01, 13.40)	6.03 (0.06, 985.20)	5.33 (0.11, 979.60)	2.25 (0.02, 784.60)	2.37 (0.03, 489.20)	—		
IM TE, 200 mg/2 wk	0.15 (0.00, 5.82)	0.04 (0.00, 2.30)	0.08 (0.00, 13.95)	1.65 (0.00, 760.10)	1.49 (0.00, 781.70)	0.58 (0.00, 673.10)	0.74 (0.00, 278.60)	0.30 (0.00, 18.63)	—	
IM TE, 250 mg/3 wk	0.15 (0.00, 13.07)	0.04 (0.00, 4.60)	0.09 (0.00, 24.03)	1.91 (0.00, 1186.00)	1.76 (0.00, 999.40)	0.72 (0.00, 718.60)	0.77 (0.00, 596.10)	0.30 (0.00, 23.49)	1.26 (0.00, 647.50)	—

TABLE 4.6: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 120 or 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/3 wk
Gel 1%, 50 mg/d	2.42 (0.63, 11.80)	—								
Gel 1%, 100 mg/d	1.52 (0.11, 22.14)	0.61 (0.03, 13.11)	—							
Gel 1.62%, 40 mg/d	0.36 (0.01, 9.95)	0.14 (0.00, 5.29)	0.23 (0.00, 14.45)	—						
Gel 2%, 60 mg/d	0.24 (0.01, 3.53)	0.09 (0.00, 2.04)	0.14 (0.00, 6.92)	0.60 (0.01, 44.76)	—					
Oral TU 120 mg/d	0.50 (0.01, 11.87)	0.20 (0.00, 5.83)	0.32 (0.00, 18.43)	1.36 (0.01, 136.10)	2.10 (0.02, 267.90)	—				
Oral TU 120 or 160 mg/d	0.49 (0.01, 13.46)	0.19 (0.00, 7.52)	0.30 (0.00, 24.13)	1.32 (0.01, 140.70)	2.16 (0.02, 214.70)	0.97 (0.01, 170.70)	—			
IM TU, 1000 mg/12 wk	0.66 (0.15, 2.59)	0.26 (0.03, 1.88)	0.43 (0.02, 8.29)	1.86 (0.04, 52.83)	2.82 (0.12, 115.90)	1.29 (0.04, 85.74)	1.41 (0.03, 88.29)	—		
IM TE, 200 mg/2 wk	0.53 (0.04, 6.33)	0.21 (0.01, 3.85)	0.34 (0.01, 13.52)	1.43 (0.02, 74.77)	2.29 (0.05, 149.80)	1.06 (0.02, 117.80)	1.12 (0.01, 109.30)	0.82 (0.04, 14.18)	—	
IM TE, 250 mg/3 wk	0.41 (0.01, 13.71)	0.16 (0.00, 7.15)	0.27 (0.00, 18.98)	1.09 (0.01, 115.70)	1.86 (0.01, 195.60)	0.85 (0.00, 157.40)	0.86 (0.01, 143.80)	0.64 (0.01, 18.85)	0.79 (0.01, 61.29)	—

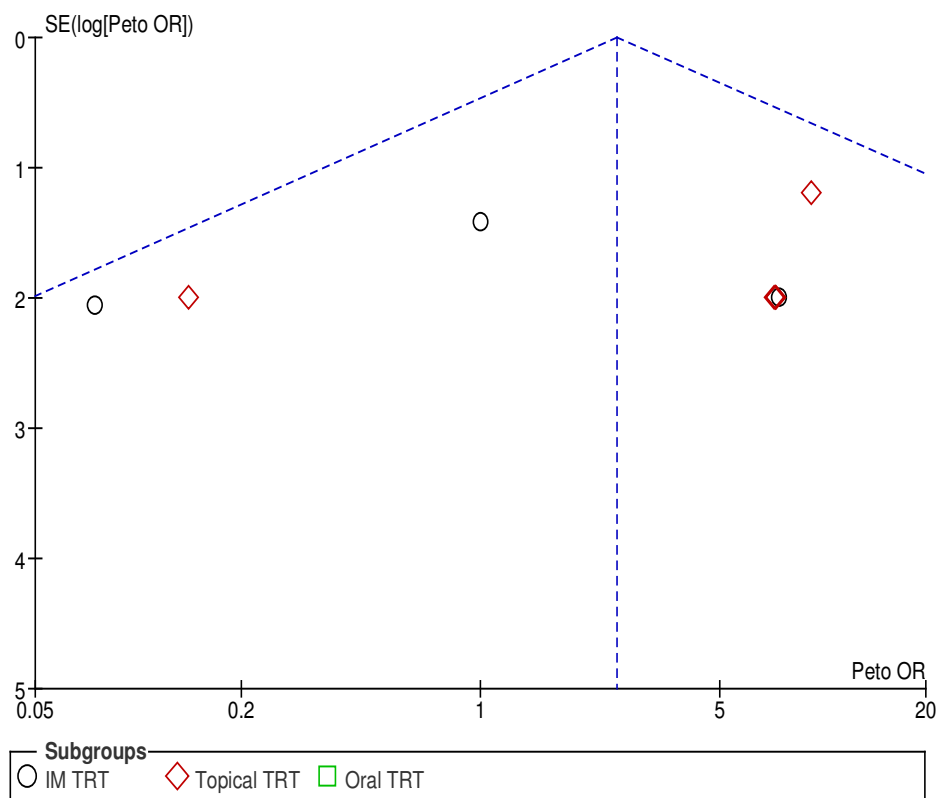
TABLE 4.7: CARDIOVASCULAR DEATH — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED

	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	IM TU, 1000 mg/12wk
Gel 1%, 50 mg/d	2.43 (0.59, 11.54)	—		
Gel 1%, 100 mg/d	1.49 (0.10, 21.29)	0.60 (0.03, 12.84)	—	
IM TU, 1000 mg/12 wk	0.62 (0.09, 3.42)	0.25 (0.02, 2.31)	0.42 (0.02, 10.50)	—

PUBLICATION BIAS

To investigate the possibility of publication bias, the standard error of the log odds ratio was plotted against the odds ratio for each of the trials that reported cardiovascular death. The standard error was relatively consistent for each trial and does not appear to be associated with the summary odds ratio (Figure 4.5), suggesting a low likelihood of publication bias.

FIGURE 4.5: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — CARDIOVASCULAR DEATH



INFLUENCE OF FUNDING

Of the trials that reported cardiovascular death, 4 reported no industry funding (3, 27, 33, 36), while the remainder reported mixed industry and non-industry, industry only, or did not report the funding source. There was insufficient data to perform a network meta-analysis involving only these trials. Of the 4 trials, cardiovascular death was only reported in 1 trial (3), with 1 event in the 1% testosterone group (n = 103) and zero events in the placebo group (n = 106), giving an odds ratio of 7.18 (95% CI 0.14 to 362.14).

RISK OF BIAS

Of the 15 trials that reported cardiovascular death, 3 were judged to be at low overall risk of bias (adequate allocation concealment, blinding, outcome data addressed) (29, 31, 33). In these 3 trials, 1 cardiovascular event was reported in the placebo arm (n = 106), and zero events were reported in the testosterone arms (n = 309), giving an odds ratio of 0.01 (95% CI 0.00 to 1.41). There were insufficient data to perform network meta-analysis for trials at low overall risk of bias.

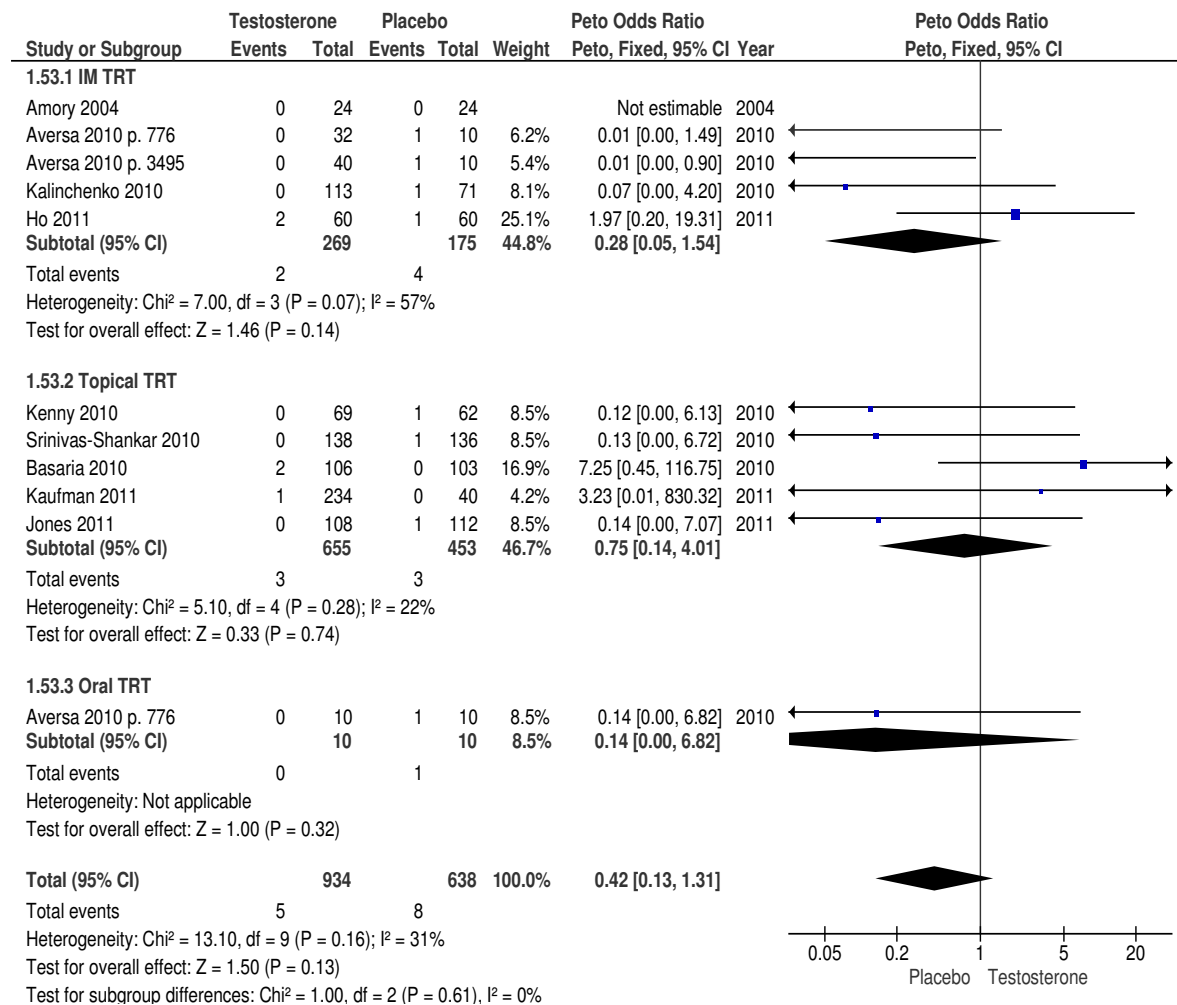
MYOCARDIAL INFARCTION

In total, 10 trials reported myocardial infarction during the treatment period (3, 28, 30-32, 36, 41-44). When compared by pairwise meta-analysis, there was no significant difference in the odds of myocardial infarction among participants taking any testosterone product compared with placebo (OR 0.45, 95% CI 0.14 to 1.50; $I^2 = 41\%$) (Figure 4.6).

Our network meta-analysis for myocardial infarction included 10 trials involving 1562 participants and 8 treatments (Figure 4.7).

Compared with placebo, there was no significant difference in the odds of myocardial infarction for any of the testosterone replacement therapies included in the network (Table 4.8). There were no significant differences in the odds among the treatments. However, the credible intervals of some estimates were very wide, likely because of the zero event counts within the network.

FIGURE 4.6: ODDS RATIO OF MYOCARDIAL INFARCTION AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY*



*Aversa 2010, p. 776, was a 3-arm trial involving placebo, IM and oral testosterone undecanoate. The placebo group is counted under both IM and oral, giving a slightly different odds ratio in the figure above compared to when the placebo group is not entered twice.

FIGURE 4.7: EVIDENCE NETWORK FOR MYOCARDIAL INFARCTION

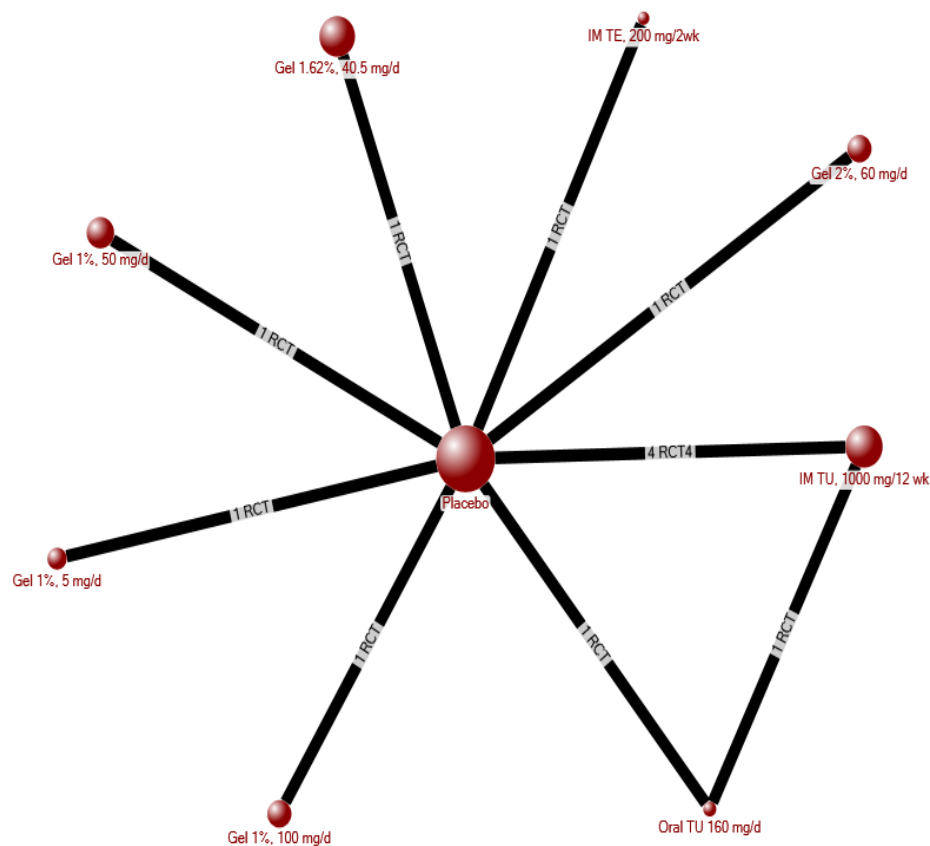


TABLE 4.8: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1 %, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2% 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk
Gel 1%, 5 mg/d	0.08 (0.00, 3.23)	—							
Gel 1%, 50 mg/d	0.08 (0.00, 2.96)	1.01 (0.00, 408.50)	—						
Gel 1%, 100 mg/d	3.25 (0.20, 73.74)	43.78 (0.39, 13850.00)	41.26 (0.39, 12040.00)	—					
Gel 1.62%, 40 mg/d	0.56 (0.02, 18.65)	7.46 (0.05, 2541.00)	6.95 (0.05, 2349.00)	0.16 (0.00, 14.67)	—				
Gel 2%, 60 mg/d	0.10 (0.00, 3.38)	1.12 (0.00, 376.00)	1.15 (0.00, 380.90)	0.03 (0.00, 2.80)	0.17 (0.00, 21.67)	—			
Oral TU 160 mg/d	0.11 (0.00, 5.49)	1.38 (0.00, 498.00)	1.40 (0.00, 540.70)	0.03 (0.00, 4.73)	0.19 (0.00, 33.68)	1.18 (0.00, 701.70)	—		
IM TU, 1000 mg/12 wk	0.18 (0.02, 1.00)	2.18 (0.03, 380.00)	2.15 (0.03, 348.20)	0.05 (0.00, 1.43)	0.31 (0.01, 12.85)	1.88 (0.03, 494.50)	1.52 (0.02, 289.00)	—	
IM TE, 200 mg/2 wk	0.22 (0.00, 15.78)	2.82 (0.01, 1437.00)	2.68 (0.00, 1694.00)	0.06 (0.00, 12.33)	0.38 (0.00, 81.30)	2.34 (0.00, 1989.00)	2.11 (0.00, 1422.00)	1.26 (0.00, 150.60)	—

We next applied an adjusted continuity correction to all cells with zero counts to try to improve the precision of the credible intervals. Following adjustment, there was no significant difference between any testosterone treatment and placebo, and there were no significant differences among the treatments (Table 4.9).

TABLE 4.9: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1 %, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2% 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk
Gel 1%, 5 mg/d	0.26 (0.01, 4.18)	—							
Gel 1%, 50 mg/d	0.25 (0.01, 4.13)	0.98 (0.01, 68.23)	—						
Gel 1%, 100 mg/d	2.45 (0.23, 38.53)	10.11 (0.24, 785.80)	10.90 (0.25, 1078.00)	—					
Gel 1.62%, 40 mg/d	0.73 (0.05, 15.62)	3.04 (0.06, 239.00)	3.24 (0.05, 327.40)	0.29 (0.01, 14.45)	—				
Gel 2%, 60 mg/d	0.26 (0.01, 3.72)	1.01 (0.01, 74.16)	1.07 (0.01, 99.67)	0.10 (0.00, 3.75)	0.33 (0.00, 17.20)	—			
Oral TU 160 mg/d	0.50 (0.01, 8.96)	1.86 (0.02, 175.70)	2.07 (0.02, 205.90)	0.19 (0.00, 8.32)	0.66 (0.01, 34.63)	1.98 (0.02, 205.10)	—		
IM TU, 1000 mg/12 wk	0.27 (0.05, 1.03)	1.01 (0.04, 44.17)	1.06 (0.04, 56.73)	0.10 (0.00, 1.74)	0.35 (0.01, 7.30)	1.04 (0.04, 51.62)	0.52 (0.03, 20.35)	—	
IM TE, 200 mg/2 wk	0.54 (0.01, 14.15)	2.10 (0.02, 257.40)	2.17 (0.02, 286.80)	0.20 (0.00, 11.82)	0.70 (0.00, 48.97)	2.14 (0.02, 260.50)	1.07 (0.01, 114.80)	2.01 (0.03, 73.92)	—

In an attempt to further refine the estimate of the odds of myocardial infarction associated with the use of testosterone replacement therapy, we excluded from the network any treatments with zero events. This resulted in a much smaller network, comprised of 3 treatments. There was no significant difference between any testosterone treatment and placebo, and there were no significant differences among the treatments (Table 4.10).

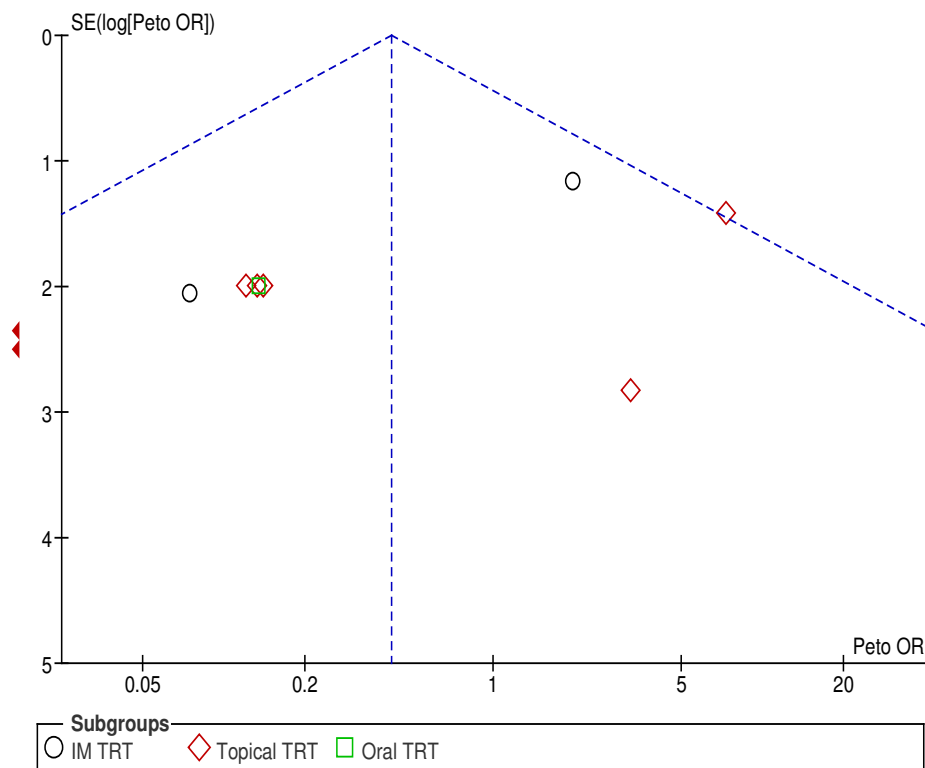
TABLE 4.10: MYOCARDIAL INFARCTION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED

	Placebo	Gel 1 %, 100 mg/d	Gel 1.62%, 40.5 mg/d	IM TU, 1000 mg/12wk
Gel 1%, 100 mg/d	2.56 (0.25, 35.03)	—		
Gel 1.62%, 40.5 mg/d	0.72 (0.05, 16.19)	0.28 (0.01, 13.92)	—	
IM TU, 1000 mg/12 wk	0.43 (0.08, 2.08)	0.17 (0.01, 2.72)	0.58 (0.02, 13.51)	—

PUBLICATION BIAS

The standard error of the log odds ratio was plotted against the odds ratio for each of the 10 trials that reported myocardial infarction. The spread of the data points in Figure 4.8 follows a general funnel shape, which is suggestive of no publication bias.

FIGURE 4.8: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — MYOCARDIAL INFARCTION



INFLUENCE OF FUNDING

Of the 10 trials that reported myocardial infarction during the treatment period, 2 reported having no industry funding (3, 36), while the others reported having industry funding, having a mix of industry and non-industry, or did not report the funding source. Zero myocardial infarctions were reported in either the placebo or intramuscular testosterone enanthate arm ($n = 24$ in each) in the trial by Amory and colleagues (36). Two events were reported in the 1% testosterone gel group ($n = 106$) and zero events in the placebo group ($n = 103$) in the trial by Basaria and colleagues (3), giving an odds ratio of 7.25 (95% CI 0.45 to 116.75).

RISK OF BIAS

Of the 10 trials that reported myocardial infarction, 3 were judged to be at low overall risk of bias (28, 29, 31). In these 3 trials, 2 events were reported in the placebo arm ($n = 171$), and 3 events were reported in the testosterone arms ($n = 407$), giving an odds ratio of 1.03 (95% CI 0.16 to 6.68). There were insufficient data to perform network meta-analysis for trials at low overall risk of bias.

STROKE

Four trials reported stroke during the treatment period (3, 35, 36, 45). There were insufficient data to perform network meta-analysis. In the meta-analysis of data from placebo-controlled trials, there was no significant difference in the odds of stroke between any testosterone replacement therapy and placebo (OR 0.50, 95% CI 0.05 to 4.85; $I^2 = 25\%$) (Figure 4.9).

There were insufficient data to perform network meta-analysis for the risk of stroke associated with the use of testosterone replacement products.

PUBLICATION BIAS

The standard error of the log odds ratio was plotted against the odds ratio for each of the 4 trials that reported stroke. Of the studies plotted in the figure below, there does not seem to be a relationship between the odds ratio and the standard error, in that trials showing either a positive or negative effect of testosterone on the risk of stroke were associated with a similar standard error (Figure 4.10). However, this funnel plot was constructed with data from only 3 trials, making assessment of asymmetry unreliable (14).

FIGURE 4.9: ODDS RATIO OF STROKE AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY

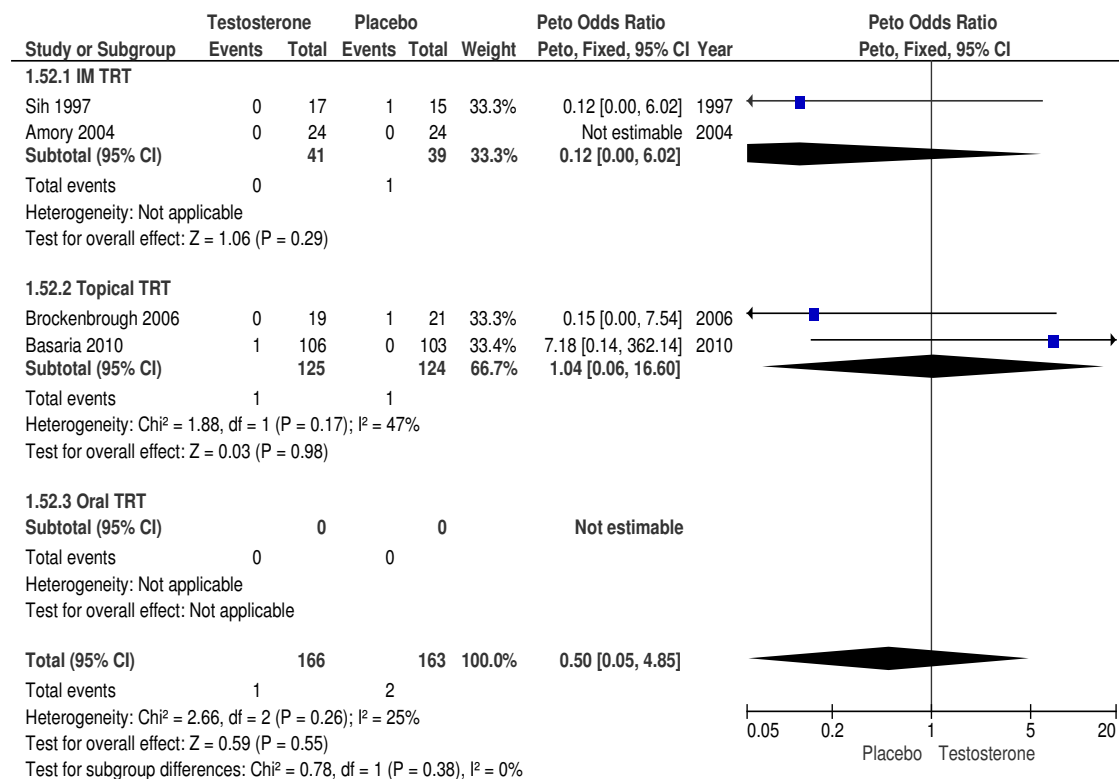
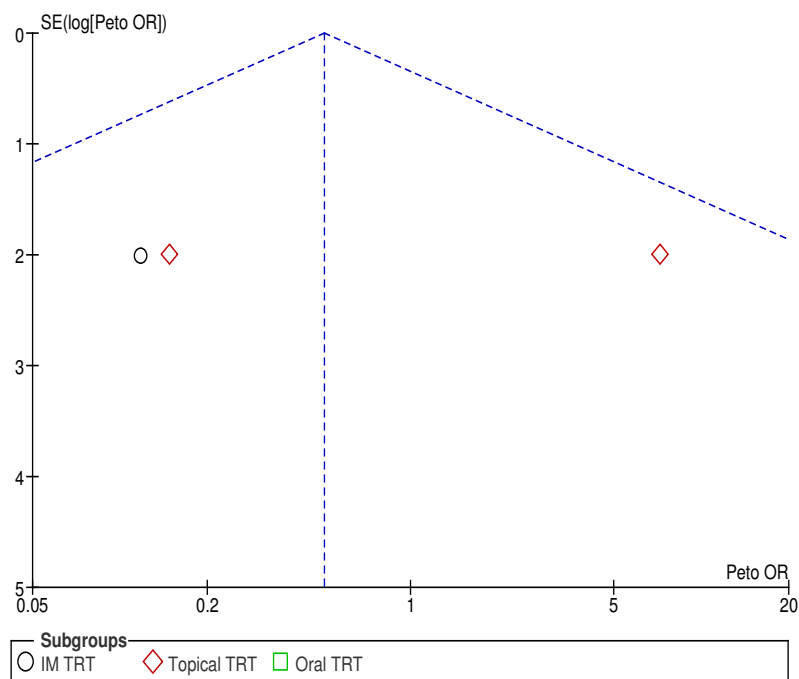


FIGURE 4.10: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — STROKE



INFLUENCE OF FUNDING

Of the 4 trials that reported stroke, 2 reported having no industry funding (3, 36). In the trial by Amory and colleagues (36), zero events were reported in either the placebo or intramuscular testosterone enanthate arms ($n = 24$ in each arm). Basaria and colleagues (3) reported that 1 participant in the 1% testosterone gel group ($n = 106$) experienced a stroke, while zero participants in the placebo group ($n = 103$) experienced a stroke, giving an odds ratio in the testosterone group of 7.18 (95% CI 0.14 to 365.14).

RISK OF BIAS

Of the 4 trials that reported myocardial infarction, none were judged to be at low overall risk of bias.

PROSTATE CANCER

Eleven trials reported newly diagnosed prostate cancer among participants (3, 26, 32, 36, 44, 46-51). Of these, 10 involved comparison of a testosterone product with placebo. In the pairwise meta-analysis involving these 10 trials, the overall odds of prostate cancer associated with the use of any type of testosterone replacement therapy was 0.78 (95% CI 0.31 to 1.99; $I^2 = 27\%$;) (Figure 4.11).

In order to compare the risk of prostate cancer among the products, we performed a network meta-analysis. All 11 trials that reported prostate cancer during the treatment period were included, resulting in 16 comparisons based on 10 trials with 2 arms and 1 trial with 4 arms. The network involved 9 testosterone replacement products and 2028 participants (Figure 4.12).

Compared with placebo, there were no significant differences in the odds of prostate cancer associated with the use of any testosterone replacement therapy (Table 4.11). In the head-to-head comparison, oral testosterone undecanoate (160 mg/d) was associated with a lower odds of prostate cancer compared with testosterone patch (5 mg/d) (OR 0.01, 95% credible interval 0.00 to 0.67). Oral testosterone undecanoate was also associated with a significantly better odds compared with intramuscular testosterone enanthate (200 mg/2 wk); however, this estimate was associated with a wide credible interval.

FIGURE 4.11: ODDS RATIO OF PROSTATE CANCER AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY

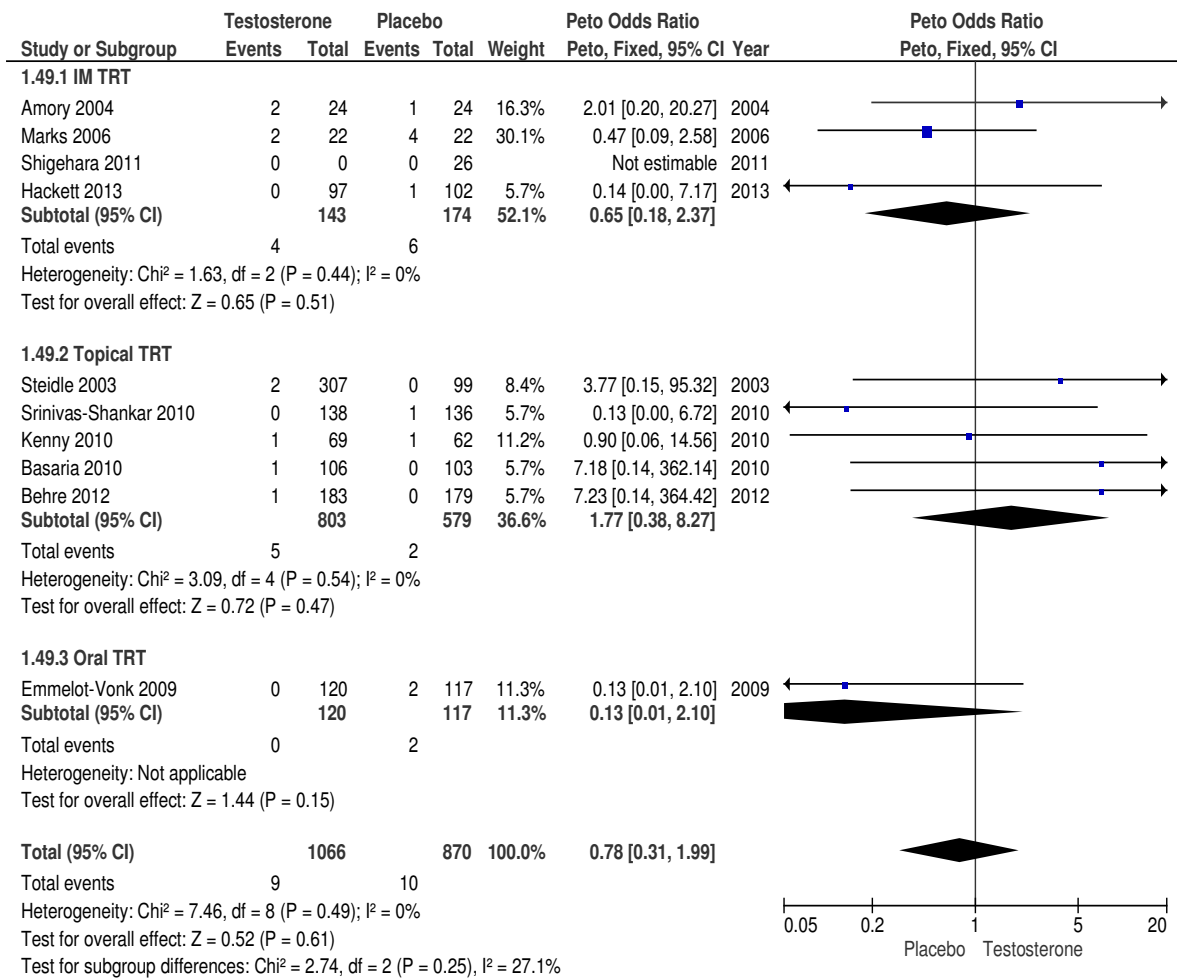


FIGURE 4.12: EVIDENCE NETWORK FOR PROSTATE CANCER

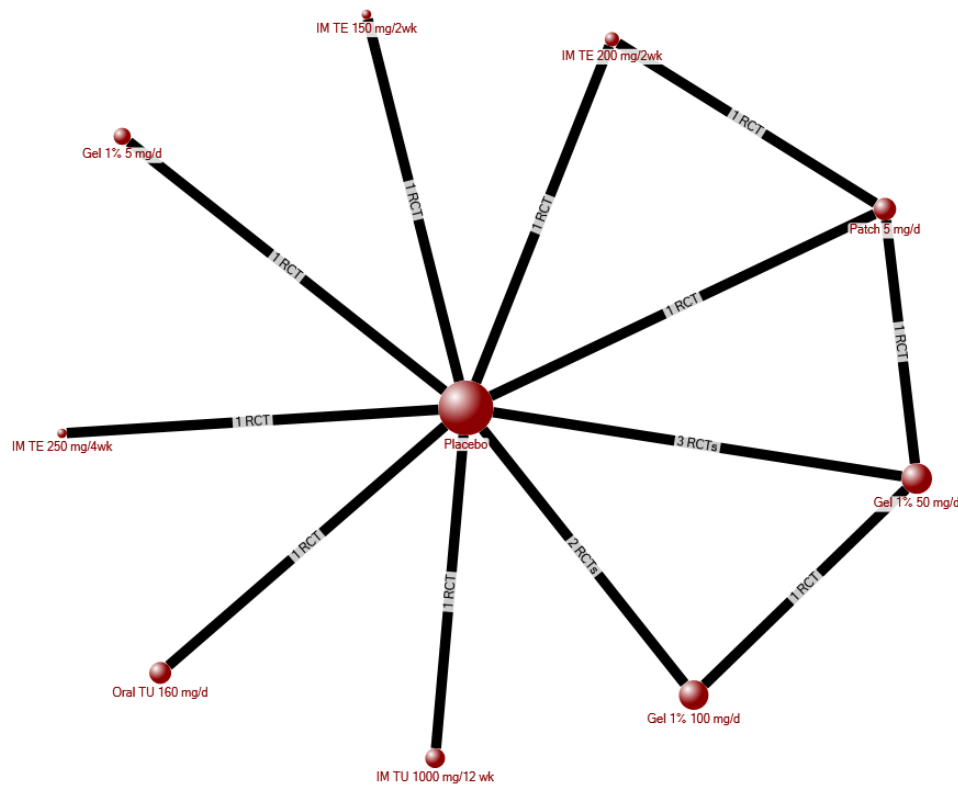


TABLE 4.11: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch 5 mg/d	Gel 1%, 5 mg/d	Gel 1% 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 150 mg/2wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/4 wk
Patch 5 mg/d	7.36 (0.66, 129.00)	—								
Gel 1%, 5 mg/d	0.96 (0.04, 22.24)	0.12 (0.00, 6.93)	—							
Gel 1% 50 mg/d	0.66 (0.04, 8.90)	0.09 (0.00, 2.21)	0.70 (0.01, 37.31)	—						
Gel 1%, 100 mg/d	1.41 (0.06, 32.28)	0.20 (0.00, 4.60)	1.54 (0.02, 119.30)	2.17 (0.05, 110.80)	—					
Oral TU 160 mg/d	0.08 (0.00, 2.11)	0.01* (0.00, 0.67)	0.07 (0.00, 7.20)	0.11 (0.00, 9.33)	0.05 (0.00, 5.41)	—				
IM TU, 1000 mg/12 wk	0.14 (0.00, 6.83)	0.02 (0.00, 1.93)	0.14 (0.00, 21.32)	0.21 (0.00, 25.28)	0.09 (0.00, 15.41)	1.96 (0.00, 726.20)	—			
IM TE, 150 mg/2wk	0.45 (0.05, 3.76)	0.06 (0.00, 1.53)	0.46 (0.01, 22.35)	0.67 (0.02, 22.70)	0.31 (0.01, 13.41)	6.03 (0.11, 971.10)	3.33 (0.04, 741.00)	—		
IM TE, 200 mg/2 wk	5.99 (0.65, 91.39)	0.84 (0.07, 9.18)	6.74 (0.12, 347.60)	9.28 (0.35, 414.10)	4.29 (0.14, 198.70)	89.45* (1.36, 19420.00)	47.38 (0.46, 11490.00)	13.84 (0.59, 429.50)	—	
IM TE, 250 mg/4 wk	0.99 (0.00, 438.50)	0.12 (0.00, 94.67)	0.98 (0.00, 1017.00)	1.51 (0.00, 1268.00)	0.67 (0.00, 623.00)	12.97 (0.01, 32540.00)	7.98 (0.00, 13500.00)	2.20 (0.00, 1325.00)	0.15 (0.00, 105.70)	—

Following adjusted continuity correction to account for zero event counts in the network, the differences between oral testosterone undecanoate and testosterone patch or intramuscular testosterone enanthate were no longer significant (Table 4.12).

TABLE 4.12: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Patch 5 mg/d	Gel 1%, 5 mg/d	Gel 1% 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 150 mg/2wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/4 wk
Patch 5 mg/d	2.63 (0.38, 20.55)	—								
Gel 1%, 5 mg/d	0.61 (0.03, 9.09)	0.23 (0.01, 6.19)	—							
Gel 1% 50 mg/d	0.56 (0.09, 2.87)	0.21 (0.02, 2.14)	0.93 (0.04, 23.22)	—						
Gel 1%, 100 mg/d	0.81 (0.09, 6.07)	0.31 (0.02, 3.21)	1.35 (0.04, 49.21)	1.45 (0.10, 20.24)	—					
Oral TU 160 mg/d	0.17 (0.01, 2.18)	0.06 (0.00, 1.74)	0.28 (0.00, 12.88)	0.31 (0.01, 6.23)	0.20 (0.00, 6.92)	—				
IM TU, 1000 mg/12 wk	0.27 (0.01, 4.12)	0.10 (0.00, 2.94)	0.43 (0.00, 21.55)	0.48 (0.01, 13.15)	0.32 (0.00, 10.33)	1.54 (0.02, 121.90)	—			
IM TE, 150 mg/2wk	0.44 (0.05, 3.15)	0.16 (0.01, 2.66)	0.72 (0.03, 26.81)	0.78 (0.05, 12.46)	0.53 (0.03, 9.84)	2.63 (0.09, 132.80)	1.68 (0.05, 103.80)	—		
IM TE, 200 mg/2 wk	2.54 (0.37, 18.99)	0.96 (0.13, 7.14)	4.27 (0.15, 144.50)	4.59 (0.42, 61.23)	3.13 (0.23, 53.26)	15.33 (0.57, 932.00)	9.85 (0.33, 722.30)	5.92 (0.37, 99.96)	—	
IM TE, 250 mg/4 wk	0.53 (0.01, 13.77)	0.19 (0.00, 7.63)	0.83 (0.01, 61.46)	0.92 (0.02, 38.30)	0.64 (0.01, 31.74)	3.14 (0.03, 353.00)	1.99 (0.02, 244.70)	1.16 (0.02, 57.94)	0.20 (0.00, 8.57)	—

In the network which involved only treatments for which at least 1 case of prostate cancer had been reported, there were no significant differences between placebo and any of the included testosterone treatments, and there were no significant differences among the treatments (Table 4.13).

TABLE 4.13: PROSTATE CANCER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED

	Placebo	Patch 5 mg/d	Gel 1%, 5 mg/d	Gel 1% 50 mg/d	Gel 1%, 100 mg/d	IM TE, 150 mg/2wk	IM TE, 200 mg/2 wk
Patch 5 mg/d	2.88 (0.42, 20.23)	—					
Gel 1%, 5 mg/d	0.64 (0.03, 9.38)	0.22 (0.01, 6.53)	—				
Gel 1% 50 mg/d	0.58 (0.08, 2.85)	0.20 (0.01, 2.13)	0.91 (0.03, 25.01)	—			
Gel 1%, 100 mg/d	0.82 (0.08, 5.36)	0.29 (0.02, 3.04)	1.27 (0.04, 38.86)	1.43 (0.10, 19.81)	—		
IM TE, 150 mg/2wk	0.43 (0.05, 2.97)	0.15 (0.01, 2.30)	0.67 (0.02, 22.28)	0.76 (0.05, 10.93)	0.52 (0.03, 10.11)	—	
IM TE, 200 mg/2 wk	2.73 (0.38, 21.45)	0.94 (0.12, 7.25)	4.26 (0.15, 164.00)	4.89 (0.37, 71.65)	3.34 (0.25, 60.92)	6.25 (0.41, 125.90)	—

The standard error of the log odds ratio was plotted against the odds ratio for each of the 11 trials that reported prostate cancer. In general, the odds ratios are evenly distributed above and below the point estimate (indicated by the vertical dashed line), regardless of the standard error (Figure 4.13), suggesting that the possibility of publication bias for this outcome is low.

SE(log[Peto OR])

Peto OR

Subgroups

- IM TRT
- Topical TRT
- Oral TRT

Of the 11 trials that reported prostate cancer, 3 reported having no industry funding (3, 36, 48). In total, 3 men in the placebo group (n = 244) and 3 men in the testosterone group (n = 240) developed prostate cancer, giving an odds ratio of 0.99 (95% CI 0.20 to 4.98; $I^2 = 41\%$).

RISK OF BIAS

Of the 11 trials that reported prostate cancer, 2 were judged to be at low overall risk of bias (46, 48). In these 2 trials, 3 events were reported in the placebo arm ($n = 219$), and zero events were reported in the testosterone arms ($n = 207$), giving an odds ratio of 0.13 (95% CI 0.01 to 1.30; $I^2 = 0\%$). There were insufficient data to perform network meta-analysis involving only trials at low overall risk of bias.

SERIOUS ADVERSE EVENTS

Thirteen trials reported serious adverse events during the treatment period (3, 26, 28, 32, 39, 41, 42, 46, 48, 52-55). In the pairwise meta-analysis of any testosterone product ($k = 11$ trials), there was no increased odds of a serious adverse event associated with the use of testosterone replacement therapy (OR 1.03, 95% CI 0.66 to 1.61; $I^2 = 4\%$) (Figure 4.15).

The network meta-analysis for serious adverse events included 2184 participants taking 9 testosterone treatments in 13 trials. Of these, 12 trials involved 2 arms, and 1 trial involved 3 arms, giving 15 direct comparisons in the network (Figure 4.14).

FIGURE 4.14: EVIDENCE NETWORK, SERIOUS ADVERSE EVENTS

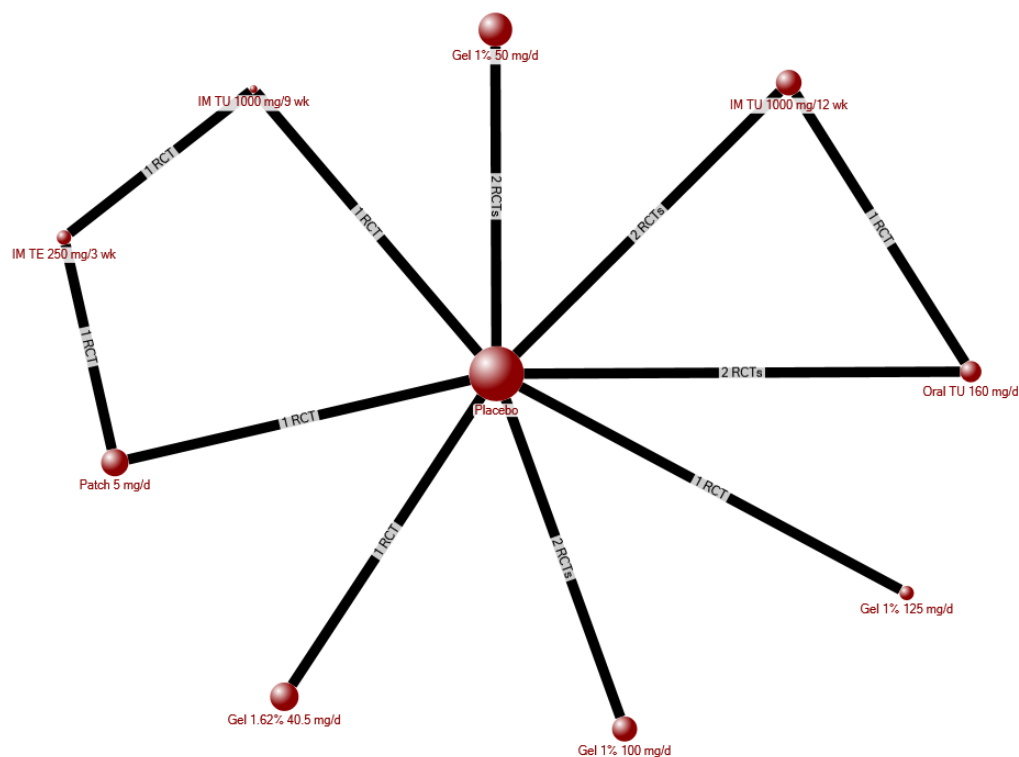
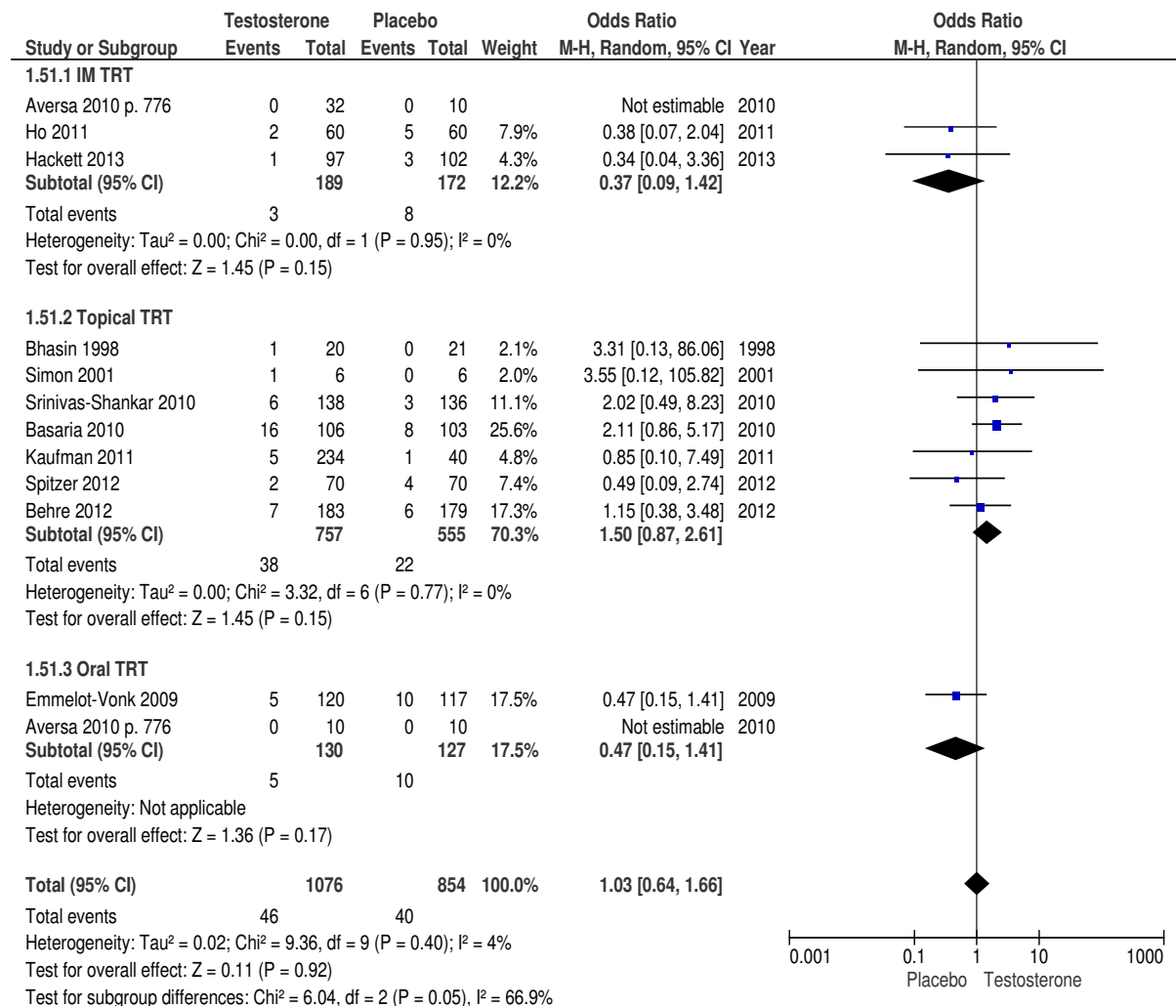


FIGURE 4.15: ODDS RATIO OF A SERIOUS ADVERSE EVENT AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY, BY ROUTE



There were no significant differences in the odds of a serious adverse event between any testosterone replacement therapy and placebo (Table 4.14). There were no significant differences among the treatments; however, the odds ratios for several comparisons had very wide credible intervals.

To attempt to account for the wide credible intervals, we adjusted each zero event count in the network using an adjusted continuity correction and re-analyzed the data. Addition of the continuity correction resulted in more narrow credible intervals for most treatments (Table 4.15). The results of this analysis were consistent with the base-case analysis: there were no

significant differences in the odds of a serious adverse event between any testosterone treatment and placebo or among the treatments.

Of the treatments involved in the network, 1 treatment had zero reported serious adverse events (IM TU 1000/9 wk). The credible intervals associated with this treatment in the network were wide; we thus re-analyzed the data after removing this treatment from the network. The removal of this treatment from the network resulted in narrower credible intervals for some treatments but did not change the significance of any estimate (Table 4.16).

TABLE 4.14: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1%, 125 mg/d	Gel 1.62%, 40.5 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/ 9 wk	IM TU, 1000 mg/12 wk	IM TE, 250 mg/ 3 wk
Patch, 5 mg/d	1.14 (0.06, 15.71)	—								
Gel 1%, 50 mg/d	1.35 (0.48, 3.86)	1.18 (0.07, 26.32)	—							
Gel 1%, 100 mg/d	1.35 (0.47, 3.41)	1.18 (0.07, 24.46)	1.00 (0.22, 3.95)	—						
Gel 1%, 125 mg/d	2.57 (0.10, 98.48)	2.51 (0.04, 200.90)	1.90 (0.06, 80.61)	1.93 (0.07, 84.36)	—					
Gel 1.62%, 40.5 mg/d	0.74 (0.11, 7.32)	0.66 (0.03, 24.88)	0.56 (0.06, 6.53)	0.56 (0.07, 6.86)	0.17 (0.00, 5.59)	—				
Oral TU 160 mg/d	0.43 (0.10, 1.62)	0.38 (0.02, 9.17)	0.32 (0.05, 1.74)	0.32 (0.06, 1.74)	2.44 (0.01, 1316.00)	0.57 (0.04, 5.62)	—			
IM TU, 1000 mg/9 wk	6.31 (0.06, 1541.00)	5.33 (0.05, 1846.00)	4.69 (0.04, 1207.00)	4.76 (0.04, 1221.00)	0.11 (0.00, 3.52)	8.02 (0.04, 2338.00)	15.33 (0.12, 4135.00)	—		
IM TU, 1000 mg/12 wk	0.29 (0.06, 1.16)	0.25 (0.01, 7.01)	0.21 (0.03, 1.23)	0.21 (0.03, 1.24)	0.52 (0.00, 38.90)	0.38 (0.02, 4.08)	0.67 (0.09, 4.84)	0.04 (0.00, 6.42)	—	
IM TE, 250 mg/3 wk	1.49 (0.06, 24.34)	1.36 (0.23, 6.12)	1.09 (0.04, 21.89)	1.10 (0.04, 22.14)	0.17 (0.00, 5.59)	1.92 (0.04, 54.23)	3.48 (0.11, 79.25)	0.24 (0.00, 23.82)	5.37 (0.16, 128.60)	—

TABLE 4.15: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1%, 125 mg/d	Gel 1.62%, 40.5 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/ 9 wk	IM TU, 1000 mg/12 wk	IM TE, 250 mg/ 3 wk
Patch, 5 mg/d	1.17 (0.11, 16.03)	—								
Gel 1%, 50 mg/d	1.34 (0.49, 3.73)	1.14 (0.07, 14.84)	—							
Gel 1%, 100 mg/d	1.35 (0.48, 3.47)	1.14 (0.07, 14.58)	1.00 (0.23, 3.96)	—						
Gel 1%, 125 mg/d	2.13 (0.12, 45.14)	1.77 (0.04, 87.70)	1.58 (0.08, 39.40)	1.61 (0.08, 40.83)	—					
Gel 1.62%, 40.5 mg/d	0.73 (0.11, 7.62)	0.63 (0.03, 17.52)	0.55 (0.06, 6.95)	0.56 (0.07, 7.01)	0.36 (0.01, 12.90)	—				
Oral TU 160 mg/d	0.45 (0.11, 1.55)	0.38 (0.02, 5.50)	0.33 (0.06, 1.63)	0.33 (0.07, 1.73)	0.21 (0.01, 4.72)	0.61 (0.04, 5.42)	—			
IM TU, 1000 mg/9 wk	2.90 (0.06, 201.30)	2.32 (0.06, 162.40)	2.16 (0.04, 170.20)	2.18 (0.04, 176.80)	1.35 (0.01, 241.90)	3.76 (0.04, 416.40)	6.70 (0.11, 549.70)	—		
IM TU, 1000 mg/12 wk	0.34 (0.08, 1.22)	0.28 (0.02, 4.24)	0.25 (0.04, 1.28)	0.25 (0.05, 1.33)	0.16 (0.01, 3.51)	0.45 (0.03, 4.73)	0.76 (0.12, 4.68)	0.12 (0.00, 6.24)	—	
IM TE, 250 mg/3 wk	1.65 (0.11, 27.15)	1.44 (0.25, 6.18)	1.23 (0.07, 24.17)	1.22 (0.07, 24.72)	0.78 (0.01, 42.05)	2.22 (0.06, 68.10)	3.74 (0.19, 82.25)	0.62 (0.01, 17.18)	5.08 (0.26, 108.80)	—

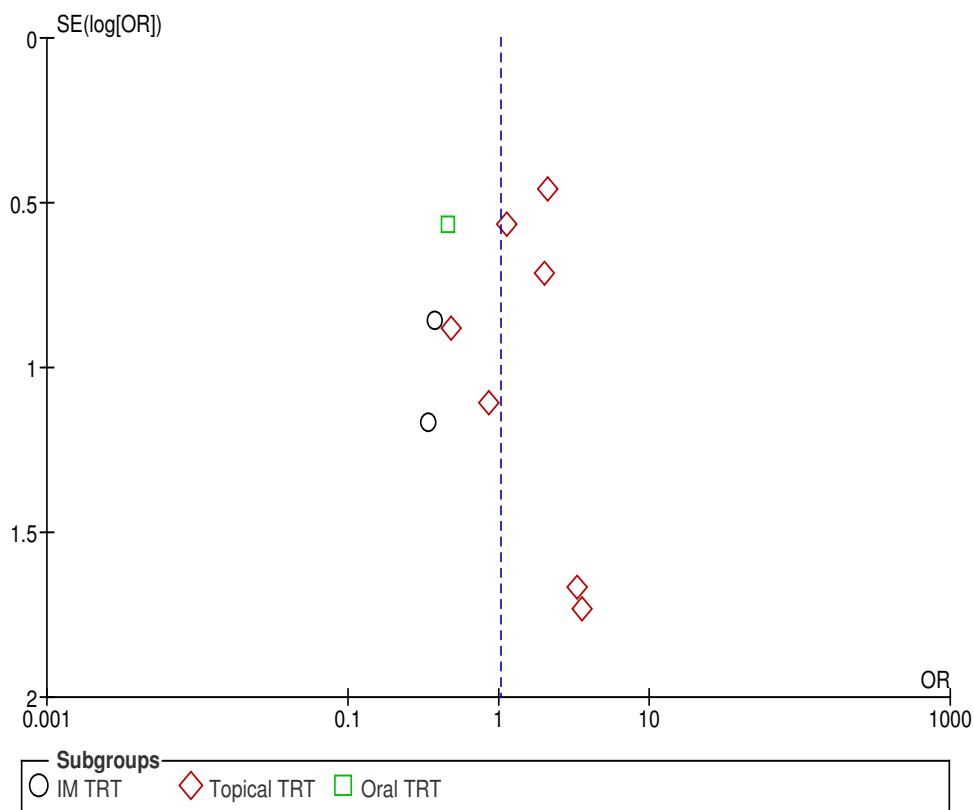
TABLE 4.16: SERIOUS ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED

	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1%, 125 mg/d	Gel 1.62%, 40.5 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 250 mg/ 3 wk
Patch, 5 mg/d	1.66 (0.14, 19.53)	—							
Gel 1%, 50 mg/d	1.33 (0.48, 3.76)	0.80 (0.05, 12.13)	—						
Gel 1%, 100 mg/d	1.33 (0.48, 3.40)	0.79 (0.06, 11.70)	1.01 (0.23, 3.95)	—					
Gel 1%, 125 mg/d	2.28 (0.11, 56.36)	1.36 (0.03, 68.85)	1.69 (0.07, 46.82)	1.73 (0.07, 47.51)	—				
Gel 1.62%, 40.5 mg/d	0.72 (0.12, 7.30)	0.46 (0.02, 11.54)	0.55 (0.07, 6.84)	0.56 (0.07, 6.56)	0.34 (0.01, 14.03)	—			
Oral TU 160 mg/d	0.45 (0.12, 1.60)	0.27 (0.02, 4.41)	0.34 (0.06, 1.74)	0.34 (0.07, 1.79)	0.20 (0.01, 4.96)	0.60 (0.04, 5.65)	—		
IM TU, 1000 mg/12 wk	0.34 (0.08, 1.25)	0.20 (0.01, 3.22)	0.26 (0.05, 1.34)	0.25 (0.05, 1.38)	0.15 (0.00, 4.00)	0.46 (0.03, 4.37)	0.76 (0.12, 4.70)	—	
IM TE, 250 mg/3 wk	2.52 (0.15, 38.99)	1.56 (0.27, 6.87)	1.90 (0.10, 35.81)	1.90 (0.10, 35.41)	1.11 (0.02, 56.53)	3.28 (0.10, 92.76)	5.61 (0.26, 118.40)	7.44 (0.34, 160.40)	—

PUBLICATION BIAS

The standard error of the log odds ratio was plotted against the odds ratio for each of the 13 trials that reported serious adverse events. The odds ratios were all close to the point estimate regardless of the standard error (Figure 4.16), suggesting that there is little evidence of publication bias for this outcome.

FIGURE 4.16: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — SERIOUS ADVERSE EVENTS



INFLUENCE OF FUNDING

Of the 13 trials that reported serious adverse events, 2 reported having no industry funding (3, 52). Overall, 12 serious adverse events were reported in the placebo group ($n = 173$), and 18 events were reported in the testosterone group ($n = 176$), giving an odds ratio of 1.52 (95% CI 0.71 to 3.28; $I^2 = 54\%$). Both the trials by Basaria and colleagues (3, 52) and Spitzer and colleagues (52) involved use of 1% testosterone gel at 100 mg/d.

RISK OF BIAS

Of the 13 trials that reported serious adverse events, 5 were judged to be at low overall risk of bias (28, 29, 31, 46, 52). In these 5 trials, 23 events were reported in the placebo arm (n = 389), and 15 events were reported in the testosterone arms (n = 581), giving an odds ratio of 0.47 (95% CI 0.23 to 0.96; $I^2 = 0\%$).

WITHDRAWALS DUE TO ADVERSE EVENTS

Withdrawals due to adverse events were reported in 40 trials (3, 26, 27, 29-40, 43-49, 51, 52, 54, 56-70). Of these, 37 involved a comparison with placebo. In the pairwise meta-analysis, the use of any testosterone product was not associated with an increased odds of withdrawal due to adverse events (OR 1.19, 95% CI 0.87 to 1.65; $I^2 = 11\%$) (Figure 4.17).

The network for withdrawals due to adverse events included 3834 participants randomized to 21 testosterone products in 40 trials. The network involved 42 comparisons, based on 39 trials with 2 arms and 1 trial with 3 arms (Figure 4.18).

FIGURE 4.17: ODDS RATIO OF WITHDRAWAL DUE TO AN ADVERSE EVENT AMONG MEN TAKING TESTOSTERONE REPLACEMENT THERAPY, BY ROUTE

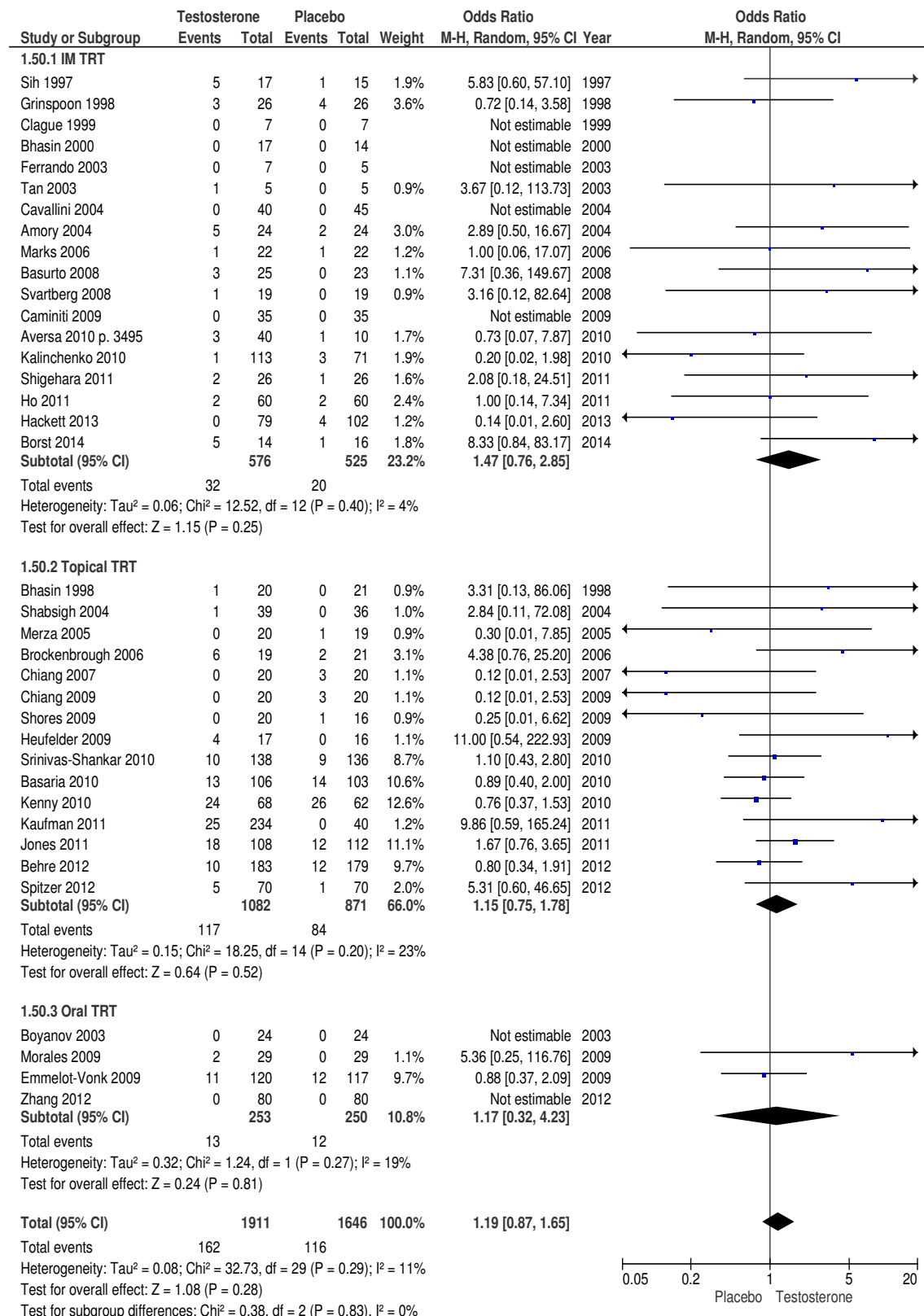
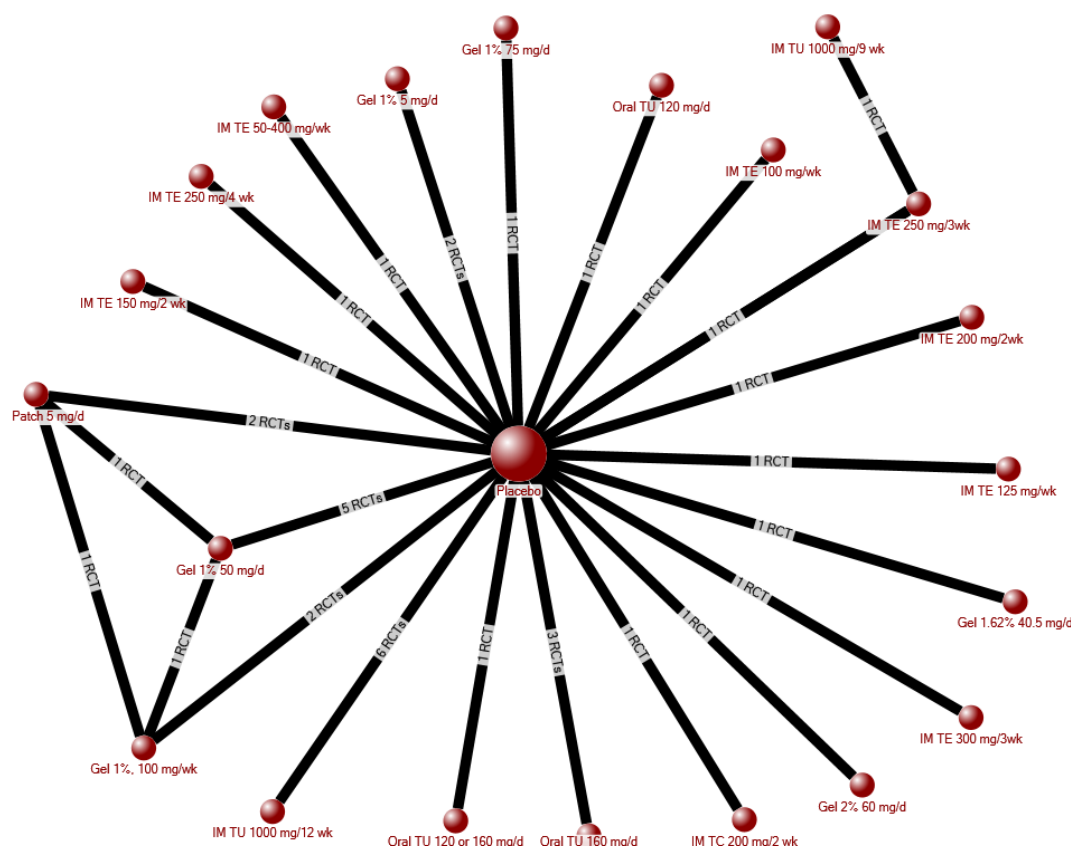


FIGURE 4.18: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS



Compared with placebo, 1.62% testosterone gel (40.5 mg/d) was associated with significantly higher odds of withdrawal due to adverse events (OR 9.83, 95% credible interval 1.93 to 193.30) (Table 4.17). There were no other significant differences compared with placebo. In the head-to-head comparisons, 1.62% testosterone gel (40.5 mg/d) was associated with significantly more withdrawals due to adverse events compared with 1% testosterone gel at either 50 or 100 mg/d or intramuscular testosterone undecanoate (1000 mg/12 wk). Testosterone patch (5 mg/d) was associated with statistically higher odds of withdrawal due to adverse events compared with intramuscular testosterone undecanoate (1000 mg/12 wk). Several of the estimates in the network were associated with wide credible intervals, likely because of zero event counts in the network (treatments for which no withdrawals were reported).

Following re-analysis in which an adjusted continuity correction had been applied to each zero event count in the network, 1.62% testosterone gel (40.5 mg/d) was still associated with a statistically higher odds of withdrawal due to adverse events compared with placebo (OR 9.51, 95% CI 1.26 to 155.90) (Table 4.18). In the head-to-head comparison, the odds of withdrawal due to adverse events were significantly higher for 1.62% testosterone gel (40.5 mg/d) compared with 1% testosterone gel at 5, 50 or 100 mg/d, and intramuscular testosterone undecanoate (1000 mg/12 wk). Consistent with the base-case analysis, testosterone patch (5 mg/d) was associated with a higher odds of withdrawal due to adverse events compared with intramuscular testosterone undecanoate (1000 mg/12 wk). Intramuscular testosterone undecanoate (1000 mg/12 wk) was associated with fewer withdrawals due to adverse events compared with intramuscular testosterone enanthate at 125 mg/wk or 200 mg/2 wk and intramuscular testosterone cypionate (200 mg/2 wk). The credible intervals associated with several comparisons were still wide in this network.

The results of network meta-analysis following removal of treatments with no reported withdrawals were consistent with the base case and continuity corrected analyses, in that 1.62% testosterone gel was associated with higher odds of withdrawal due to adverse events compared with placebo, 1% testosterone gel, and intramuscular testosterone undecanoate (1000 mg/12 wk). Intramuscular testosterone undecanoate (1000 mg/12 wk) was associated with lower odds of withdrawals due to adverse events compared with intramuscular testosterone enanthate (125 mg/wk, 200 mg/2 wk) and intramuscular testosterone cypionate (200 mg/2 wk) (Table 4.19).

TABLE 4.17: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	2.71 (0.69, 9.34)	—																				
Gel 1%, 5 mg/d	0.83 (0.28, 2.81)	0.31 (0.06, 2.05)	—																			
Gel 1%, 50 mg/d	0.85 (0.38, 1.65)	0.31 (0.09, 1.20)	1.02 (0.23, 3.58)	—																		
Gel 1%, 75 mg/d	3.61 (0.42, 40.86)	1.37 (0.12, 21.00)	4.31 (0.37, 60.78)	4.31 (0.46, 56.28)	—																	
Gel 1%, 100 mg/d	0.78 (0.27, 1.91)	0.29 (0.07, 1.20)	0.94 (0.18, 3.70)	0.92 (0.29, 2.86)	0.21 (0.02, 2.22)	—																
Gel 1.62%, 40.5 mg/d	9.83* (1.08, 193.30)	3.77 (0.29, 91.94)	11.96 (0.96, 276.10)	11.78 (1.19, 248.70)	2.87 (0.10, 109.00)	12.78 (1.18, 293.00)	—															
Gel 2%, 60 mg/d	1.61 (0.45, 5.80)	0.59 (0.11, 4.11)	1.95 (0.32, 10.28)	1.90 (0.48, 8.88)	0.44 (0.03, 5.45)	2.07 (0.45, 11.27)	0.16 (0.01, 2.09)	—														
Oral TU 120 mg/d	0.21 (0.00, 14.06)	0.08 (0.00, 6.73)	0.25 (0.00, 18.26)	0.25 (0.00, 17.70)	0.05 (0.00, 6.81)	0.27 (0.00, 20.85)	0.02 (0.00, 2.44)	0.13 (0.00, 10.58)	—													
Oral TU 160 mg/d	1.01 (0.33, 3.39)	0.37 (0.07, 2.40)	1.22 (0.24, 6.15)	1.20 (0.33, 5.32)	0.28 (0.02, 3.42)	1.31 (0.31, 6.72)	0.10 (0.00, 1.36)	0.63 (0.11, 3.63)	4.80 (0.06, 1175.00)	—												
Oral TU 120-160 mg/d	0.21 (0.00, 11.24)	0.08 (0.00, 5.29)	0.25 (0.00, 15.29)	0.25 (0.00, 14.86)	0.05 (0.00, 5.58)	0.26 (0.00, 16.89)	0.02 (0.00, 2.09)	0.13 (0.00, 8.41)	1.01 (0.00, 725.30)	0.20 (0.00, 13.52)	—											
IM TU, 1000 mg/9 wk	9.07 (0.08, 1830.00)	3.42 (0.03, 834.50)	11.01 (0.08, 2415.00)	10.83 (0.09, 2289.00)	2.45 (0.01, 683.80)	11.66 (0.10, 2556.00)	0.89 (0.00, 281.70)	5.69 (0.04, 1336.00)	50.07 (0.08, 59760.00)	8.71 (0.07, 1877.00)	54.11 (0.09, 63000.00)	—										

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
IM TU, 1000 mg/12 wk	0.37 (0.12, 1.09)	0.14* (0.03, 0.78)	0.44 (0.08, 2.09)	0.44 (0.11, 1.67)	0.10 (0.01, 1.17)	0.47 (0.11, 2.14)	0.04* (0.00, 0.45)	0.23 (0.04, 1.22)	1.73 (0.02, 441.40)	0.36 (0.07, 1.79)	1.80 (0.03, 402.00)	0.04 (0.00, 4.74)	—									
IM TE, 100 mg/wk	0.19 (0.00, 17.08)	0.07 (0.00, 8.27)	0.23 (0.00, 23.01)	0.23 (0.00, 22.83)	0.05 (0.00, 7.82)	0.25 (0.00, 25.53)	0.02 (0.00, 2.67)	0.12 (0.00, 12.83)	0.99 (0.00, 685.90)	0.19 (0.00, 19.77)	1.01 (0.00, 1841.00)	0.02 (0.00, 12.26)	0.53 (0.00, 54.54)	—								
IM TE, 125 mg/wk	6.20 (0.76, 60.80)	2.34 (0.21, 33.67)	7.51 (0.65, 90.95)	7.41 (0.83, 80.81)	1.72 (0.07, 41.05)	7.96 (0.83, 100.30)	0.61 (0.02, 15.31)	3.88 (0.33, 52.80)	30.25 (0.29, 10200.00)	6.15 (0.53, 80.78)	31.97 (0.28, 10330.00)	0.68 (0.00, 124.00)	17.10* (1.55, 222.00)	35.32 (0.23, 12740.00)	—							
IM TE, 150 mg/2 wk	0.72 (0.04, 12.02)	0.27 (0.01, 6.13)	0.86 (0.03, 17.29)	0.86 (0.04, 15.80)	0.20 (0.00, 6.59)	0.93 (0.04, 19.39)	0.07 (0.00, 2.87)	0.44 (0.02, 9.70)	3.66 (0.02, 1450.00)	0.72 (0.03, 14.20)	3.82 (0.02, 1518.00)	0.08 (0.00, 17.88)	1.97 (0.08, 39.71)	3.68 (0.02, 2014.00)	0.11 (0.00, 3.73)	—						
IM TE, 200 mg/2 wk	2.59 (0.59, 12.46)	0.97 (0.16, 6.48)	3.13 (0.45, 20.84)	3.08 (0.62, 17.25)	0.72 (0.04, 10.37)	3.37 (0.61, 21.55)	0.26 (0.01, 3.90)	1.61 (0.23, 11.98)	12.62 (0.16, 3147.00)	2.57 (0.37, 16.98)	12.84 (0.17, 3321.00)	0.28 (0.00, 42.36)	7.07* (1.15, 51.76)	14.04 (0.11, 4764.00)	0.41 (0.03, 5.91)	3.63 (0.15, 106.90)	—					
IM TE, 250 mg/3 wk	3.99 (0.36, 69.56)	1.52 (0.10, 34.89)	4.87 (0.33, 106.70)	4.81 (0.40, 95.06)	1.15 (0.03, 39.95)	5.31 (0.41, 107.60)	0.39 (0.01, 16.12)	2.49 (0.16, 56.55)	20.98 (0.17, 7124.00)	4.01 (0.27, 86.72)	21.69 (0.19, 10280.00)	0.48 (0.00, 50.85)	11.02 (0.78, 245.80)	23.47 (0.14, 9643.00)	0.66 (0.02, 22.82)	5.65 (0.14, 356.30)	1.58 (0.09, 35.45)	—				
IM TE, 250 mg/4 wk	1.56 (0.12, 18.91)	0.59 (0.03, 9.71)	1.87 (0.12, 28.50)	1.86 (0.13, 25.07)	0.42 (0.01, 11.85)	2.02 (0.14, 30.25)	0.15 (0.00, 4.43)	0.96 (0.06, 16.20)	7.52 (0.06, 2801.00)	1.53 (0.09, 24.23)	8.27 (0.06, 2768.00)	0.17 (0.00, 32.54)	4.27 (0.27, 64.61)	8.71 (0.04, 3421.00)	0.25 (0.01, 6.55)	2.13 (0.05, 108.10)	0.60 (0.03, 10.93)	0.38 (0.01, 11.94)	—			
IM TE, 300 mg/3 wk	0.69 (0.10, 4.69)	0.26 (0.03, 2.76)	0.83 (0.09, 7.36)	0.82 (0.11, 6.63)	0.19 (0.01, 3.53)	0.89 (0.11, 8.03)	0.07 (0.00, 1.32)	0.43 (0.04, 4.22)	3.30 (0.03, 1012.00)	0.67 (0.07, 6.25)	3.51 (0.04, 988.70)	0.08 (0.00, 11.77)	1.86 (0.20, 17.12)	3.69 (0.03, 1434.00)	0.11 (0.01, 1.86)	0.97 (0.03, 31.21)	0.27 (0.02, 3.00)	0.17 (0.01, 3.93)	0.43 (0.02, 10.80)	—		
IM TE, 50-400 mg/wk	0.26 (0.00, 22.45)	0.10 (0.00, 9.92)	0.30 (0.00, 30.85)	0.31 (0.00, 28.23)	0.07 (0.00, 10.28)	0.33 (0.00, 33.32)	0.02 (0.00, 4.15)	0.16 (0.00, 16.98)	1.33 (0.00, 867.40)	0.25 (0.00, 24.81)	1.39 (0.00, 1434.00)	0.03 (0.00, 16.27)	0.70 (0.00, 69.03)	1.47 (0.00, 1428.00)	0.04 (0.00, 5.46)	0.37 (0.00, 70.08)	0.10 (0.00, 11.11)	0.06 (0.00, 8.67)	0.16 (0.00, 24.32)	0.36 (0.00, 51.90)	—	
IM TC, 200 mg/2 wk	4.24 (0.54, 49.04)	1.60 (0.14, 26.24)	5.13 (0.46, 71.98)	5.05 (0.58, 68.06)	1.19 (0.05, 32.88)	5.52 (0.58, 79.53)	0.43 (0.01, 10.74)	2.61 (0.24, 41.97)	21.67 (0.19, 8290.00)	4.21 (0.37, 62.76)	23.29 (0.22, 6149.00)	0.47 (0.00, 84.82)	11.88* (1.09, 163.80)	23.49 (0.14, 8580.00)	0.68 (0.03, 16.72)	6.00 (0.19, 287.10)	1.65 (0.13, 29.08)	1.08 (0.03, 31.66)	2.79 (0.11, 93.18)	6.28 (0.35, 141.70)	17.41 (0.13, 5180.00)	—

TABLE 4.18: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	2.38 (0.79, 7.32)	—																				
Gel 1%, 5 mg/d	0.83 (0.32, 2.29)	0.35 (0.08, 1.68)	—																			
Gel 1%, 50 mg/d	0.88 (0.46, 1.63)	0.37 (0.11, 1.18)	1.05 (0.31, 3.25)	—																		
Gel 1%, 75 mg/d	3.51 (0.44, 41.31)	1.48 (0.15, 20.66)	4.25 (0.41, 58.35)	4.05 (0.47, 51.49)	—																	
Gel 1%, 100 mg/d	0.80 (0.32, 1.82)	0.33 (0.10, 1.14)	0.96 (0.24, 3.35)	0.91 (0.32, 2.50)	0.22 (0.02, 2.15)	—																
Gel 1.62%, 40.5 mg/d	9.51 (1.26, 155.90)	4.07 (0.40, 76.90)	11.30 (1.17, 220.30)	11.03 (1.23, 186.40)	2.68 (0.12, 92.05)	12.04 (1.35, 214.50)	—															
Gel 2%, 60 mg/d	1.64 (0.53, 5.08)	0.69 (0.14, 3.47)	1.98 (0.43, 8.36)	1.86 (0.53, 7.10)	0.46 (0.03, 5.21)	2.06 (0.53, 8.85)	0.17 (0.01, 1.72)	—														
Oral TU 120 mg/d	0.61 (0.01, 15.56)	0.25 (0.00, 8.13)	0.73 (0.01, 20.42)	0.70 (0.01, 19.06)	0.16 (0.00, 8.25)	0.78 (0.02, 21.32)	0.06 (0.00, 3.07)	0.37 (0.01, 11.56)	—													
Oral TU 160 mg/d	1.02 (0.38, 2.89)	0.43 (0.10, 1.97)	1.22 (0.30, 4.95)	1.15 (0.37, 4.09)	0.29 (0.02, 3.05)	1.27 (0.37, 5.05)	0.11 (0.01, 1.10)	0.61 (0.14, 2.90)	1.68 (0.06, 82.06)	—												
Oral TU 120- 160 mg/d	0.52 (0.01, 12.16)	0.22 (0.00, 6.34)	0.61 (0.01, 17.44)	0.59 (0.01, 15.01)	0.14 (0.00, 7.06)	0.65 (0.01, 17.79)	0.05 (0.00, 2.82)	0.30 (0.01, 9.09)	0.82 (0.01, 122.60)	0.50 (0.01, 13.86)	—											
IM TU, 1000 mg/9 wk	4.69 (0.12, 254.20)	1.92 (0.04, 121.10)	5.50 (0.13, 336.30)	5.34 (0.13, 307.90)	1.30 (0.02, 112.70)	5.99 (0.14, 341.80)	0.46 (0.00, 48.30)	2.83 (0.06, 179.00)	7.63 (0.06, 2130.00)	4.57 (0.10, 279.50)	9.97 (0.06, 2124.00)	—										

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
IM TU, 1000 mg/12 wk	0.45 (0.16, 1.16)	0.18 (0.04, 0.81)	0.53 (0.12, 2.07)	0.50 (0.15, 1.63)	0.12 (0.01, 1.26)	0.56 (0.15, 2.10)	0.05 (0.00 , 0.45)	0.27 (0.06, 1.19)	0.72 (0.02, 41.46)	0.44 (0.10, 1.73)	0.86 (0.03, 44.86)	0.09 (0.00, 3.93)	—									
IM TE, 100 mg/wk	0.55 (0.01, 12.87)	0.23 (0.01, 6.99)	0.66 (0.02, 16.93)	0.62 (0.02, 15.75)	0.14 (0.00, 7.27)	0.68 (0.02, 18.28)	0.05 (0.00, 2.54)	0.33 (0.01, 9.38)	0.88 (0.01, 114.50)	0.54 (0.01, 14.39)	1.07 (0.01, 128.50)	0.11 (0.00, 15.20)	1.25 (0.03, 33.94)	—								
IM TE, 125 mg/wk	6.16 (0.84, 55.57)	2.58 (0.26, 31.05)	7.41 (0.76, 80.35)	7.03 (0.90, 70.40)	1.73 (0.07, 38.45)	7.80 (0.88, 85.90)	0.62 (0.02, 13.10)	3.77 (0.37, 43.92)	10.44 (0.24, 761.50)	6.07 (0.63, 68.56)	12.28 (0.28, 1005.00)	1.36 (0.01, 102.00)	13.96 (1.53 , 155.40)	12.11 (0.25, 700.80)	—							
IM TE, 150 mg/2 wk	0.73 (0.04, 9.95)	0.30 (0.01, 5.08)	0.87 (0.04, 14.03)	0.83 (0.04, 11.99)	0.19 (0.00, 6.20)	0.92 (0.04, 14.93)	0.07 (0.00, 2.07)	0.44 (0.02, 7.65)	1.17 (0.01, 146.00)	0.71 (0.03, 11.55)	1.34 (0.02, 149.00)	0.15 (0.00, 14.29)	1.65 (0.07, 26.87)	1.31 (0.02, 102.10)	0.11 (0.00, 3.07)	—						
IM TE, 200 mg/2 wk	2.38 (0.67, 9.40)	1.01 (0.22, 4.94)	2.86 (0.57, 14.99)	2.72 (0.68, 12.29)	0.67 (0.04, 8.76)	3.01 (0.68, 14.57)	0.25 (0.01, 2.77)	1.46 (0.26, 8.36)	4.03 (0.12, 216.80)	2.35 (0.45, 12.54)	4.70 (0.16, 248.70)	0.52 (0.01, 25.88)	5.35 (1.14 , 29.79)	4.42 (0.14, 212.20)	0.38 (0.03, 4.28)	3.30 (0.18, 86.63)	—					
IM TE, 250 mg/3 wk	3.27 (0.42, 37.44)	1.38 (0.14, 20.97)	3.92 (0.40, 50.54)	3.75 (0.44, 44.82)	0.93 (0.04, 22.08)	4.15 (0.44, 53.17)	0.32 (0.01, 8.28)	2.01 (0.19, 27.19)	5.59 (0.13, 436.30)	3.23 (0.33, 42.24)	6.63 (0.15, 519.00)	0.75 (0.02, 19.79)	7.46 (0.76, 95.56)	6.48 (0.13, 403.60)	0.53 (0.03, 12.61)	4.82 (0.16, 184.20)	1.37 (0.11, 20.90)	—				
IM TE, 250 mg/4 wk	1.48 (0.14, 16.80)	0.64 (0.04, 9.09)	1.78 (0.14, 23.57)	1.70 (0.16, 20.89)	0.42 (0.01, 9.61)	1.89 (0.16, 24.96)	0.15 (0.00, 3.47)	0.91 (0.07, 13.22)	2.46 (0.05, 224.70)	1.47 (0.12, 20.10)	3.07 (0.05, 292.60)	0.33 (0.00, 23.16)	3.39 (0.27, 48.37)	2.95 (0.05, 173.50)	0.24 (0.01, 5.67)	2.16 (0.06, 89.66)	0.61 (0.04, 10.10)	0.44 (0.02, 10.79)	—			
IM TE, 300 mg/3 wk	0.69 (0.11, 3.92)	0.29 (0.03, 2.27)	0.83 (0.10, 5.93)	0.79 (0.12, 5.05)	0.19 (0.01, 2.87)	0.86 (0.12, 6.10)	0.07 (0.00, 1.04)	0.42 (0.05, 3.27)	1.11 (0.03, 78.38)	0.68 (0.08, 4.87)	1.38 (0.03, 88.05)	0.15 (0.00, 8.48)	1.53 (0.20, 11.83)	1.27 (0.03, 67.34)	0.11 (0.01, 1.55)	0.95 (0.04, 29.52)	0.28 (0.03, 2.51)	0.20 (0.01, 3.27)	0.45 (0.02, 8.41)	—		
IM TE, 50-400 mg/wk	0.62 (0.02, 15.24)	0.26 (0.01, 7.83)	0.74 (0.02, 21.23)	0.71 (0.02, 18.47)	0.17 (0.00, 7.91)	0.79 (0.02, 21.47)	0.06 (0.00, 2.82)	0.37 (0.01, 11.52)	1.01 (0.01, 159.70)	0.60 (0.02, 17.98)	1.31 (0.01, 140.60)	0.13 (0.00, 17.85)	1.39 (0.04, 43.58)	1.12 (0.01, 151.40)	0.10 (0.00, 4.20)	0.87 (0.01, 61.14)	0.26 (0.01, 8.14)	0.19 (0.00, 9.37)	0.40 (0.01, 24.86)	0.90 (0.02, 37.63)	—	
IM TC, 200 mg/2 wk	4.46 (0.60, 45.09)	1.87 (0.19, 25.42)	5.40 (0.53, 64.88)	5.13 (0.61, 58.82)	1.27 (0.05, 29.57)	5.64 (0.66, 68.34)	0.46 (0.02, 9.80)	2.74 (0.27, 34.84)	7.37 (0.16, 648.90)	4.40 (0.46, 52.83)	9.13 (0.21, 690.90)	0.94 (0.01, 82.03)	10.17 (1.09 , 118.90)	8.45 (0.20, 551.20)	0.71 (0.04, 14.33)	6.37 (0.22, 248.10)	1.86 (0.16, 25.94)	1.36 (0.06, 30.52)	3.07 (0.12, 82.13)	6.65(0.47, 117.40)	7.58 (0.15, 503.50)	—

TABLE 4.19: WITHDRAWALS DUE TO ADVERSE EVENTS — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION, TREATMENTS WITH ZERO EVENTS DROPPED

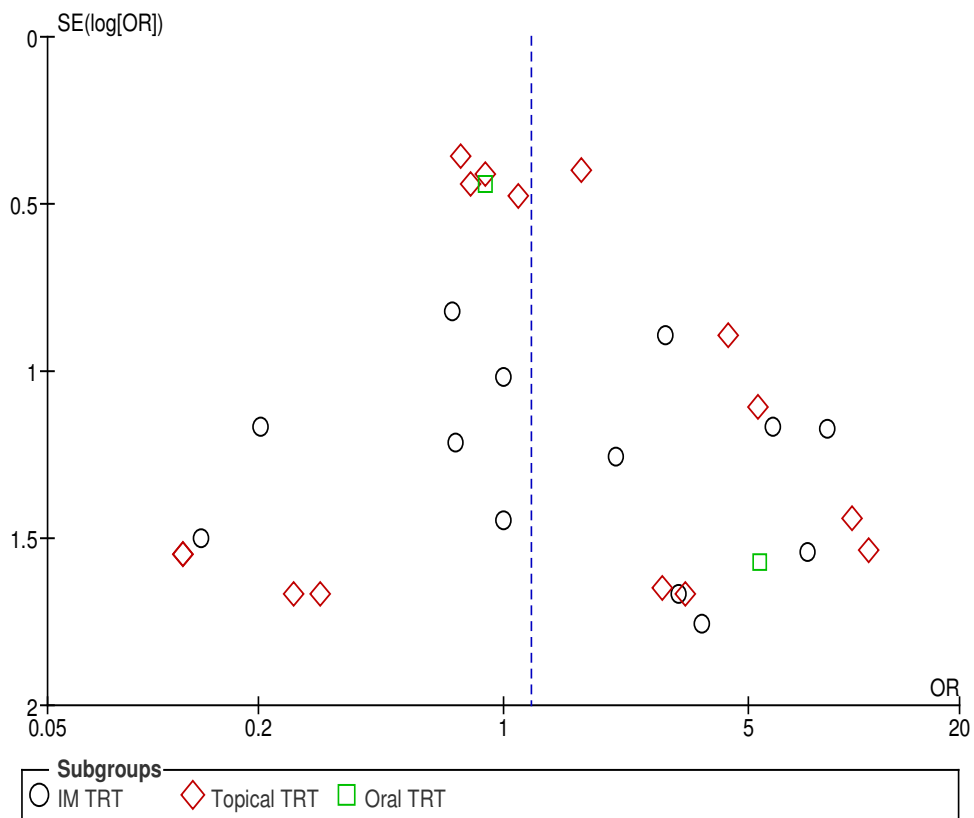
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	2.45 (0.79, 7.31)	—															
Gel 1%, 5 mg/d	0.83 (0.31, 2.32)	0.34 (0.08, 1.60)	—														
Gel 1%, 50 mg/d	0.87 (0.46, 1.61)	0.36 (0.11, 1.15)	1.05 (0.31, 3.22)	—													
Gel 1%, 75 mg/d	3.60 (0.45, 39.26)	1.50 (0.14, 20.53)	4.37 (0.43, 53.10)	4.14 (0.47, 48.50)	—												
Gel 1%, 100 mg/d	0.80 (0.33, 1.81)	0.33 (0.10, 1.10)	0.96 (0.24, 3.41)	0.91 (0.34, 2.44)	0.22 (0.02, 2.08)	—											
Gel 1.62%, 40.5 mg/d	9.31* (1.26, 178.00)	3.92 (0.38, 87.27)	11.37* (1.16, 248.80)	10.70* (1.35, 219.60)	2.68 (0.12, 89.97)	11.93* (1.31, 242.20)	—										
Gel 2%, 60 mg/d	1.62 (0.53, 5.08)	0.66 (0.15, 3.39)	1.97 (0.43, 8.62)	1.87 (0.52, 7.02)	0.45 (0.03, 5.09)	2.05 (0.52, 8.87)	0.17 (0.01, 1.80)	—									
Oral TU 160 mg/d	1.02 (0.38, 2.89)	0.42 (0.10, 1.99)	1.23 (0.31, 5.09)	1.17 (0.37, 4.11)	0.28 (0.02, 2.91)	1.28 (0.36, 5.22)	0.11 (0.01, 1.08)	0.63 (0.14, 2.94)	—								
IM TU, 1000 mg/12 wk	0.43 (0.16, 1.17)	0.18 (0.04, 0.80)	0.52 (0.12, 2.08)	0.50 (0.15, 1.62)	0.12 (0.01, 1.21)	0.54 (0.15, 2.10)	0.04* (0.00, 0.46)	0.27 (0.06, 1.16)	0.42 (0.10, 1.66)	—							

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TC, 200 mg/ 2 wk
IM TE, 125 mg/wk	5.96 (0.79, 62.05)	2.43 (0.25, 33.75)	7.22 (0.75, 88.54)	6.86 (0.83, 77.16)	1.65 (0.08, 39.04)	7.48 (0.85, 92.34)	0.61 (0.02, 14.21)	3.65 (0.37, 50.10)	5.87 (0.62, 72.39)	13.85* (1.49, 175.80)	—						
IM TE, 150 mg/2 wk	0.73 (0.04, 11.04)	0.30 (0.01, 5.43)	0.87 (0.04, 15.56)	0.84 (0.04, 13.73)	0.20 (0.00, 6.22)	0.93 (0.04, 15.61)	0.07 (0.00, 2.40)	0.45 (0.02, 8.54)	0.71 (0.03, 12.90)	1.70 (0.08, 30.34)	0.12 (0.00, 3.33)	—					
IM TE, 200 mg/2 wk	2.38 (0.66, 9.73)	0.97 (0.22, 4.85)	2.88 (0.56, 15.29)	2.74 (0.68, 12.47)	0.66 (0.04, 8.08)	3.01 (0.67, 14.99)	0.25 (0.01, 2.95)	1.47 (0.25, 8.77)	2.37 (0.44, 12.74)	5.53* (1.13, 30.54)	0.40 (0.03, 4.48)	3.25 (0.17, 85.05)	—				
IM TE, 250 mg/3 wk	4.07 (0.47, 60.27)	1.70 (0.14, 30.02)	4.95 (0.44, 89.63)	4.71 (0.50, 74.22)	1.15 (0.04, 33.64)	5.21 (0.49, 87.36)	0.44 (0.01, 11.97)	2.53 (0.22, 45.79)	4.03 (0.36, 66.58)	9.41 (0.88, 175.80)	0.68 (0.03, 22.04)	5.83 (0.18, 293.90)	1.73 (0.13, 33.29)	—			
IM TE, 250 mg/4 wk	1.57 (0.15, 20.46)	0.65 (0.05, 10.52)	1.89 (0.15, 28.44)	1.78 (0.17, 25.43)	0.43 (0.02, 11.15)	2.00 (0.17, 28.89)	0.16 (0.00, 4.16)	0.96 (0.07, 15.99)	1.54 (0.12, 23.72)	3.67 (0.29, 54.69)	0.26 (0.01, 6.42)	2.19 (0.06, 98.17)	0.66 (0.05, 10.99)	0.37 (0.01, 10.73)	—		
IM TE, 300 mg/3 wk	0.68 (0.10, 3.94)	0.28 (0.03, 2.26)	0.81 (0.10, 5.99)	0.77 (0.11, 5.07)	0.18 (0.01, 2.84)	0.85 (0.11, 6.13)	0.07 (0.00, 1.04)	0.41 (0.05, 3.38)	0.67 (0.07, 4.97)	1.58 (0.19, 11.91)	0.11 (0.01, 1.68)	0.92 (0.04, 29.16)	0.28 (0.03, 2.53)	0.16 (0.01, 2.64)	0.43 (0.02, 7.93)	—	
IM TC, 200 mg/2 wk	4.28 (0.59, 49.63)	1.79 (0.19, 25.38)	5.17 (0.57, 69.47)	4.96 (0.63, 60.52)	1.21 (0.05, 28.54)	5.47 (0.64, 71.24)	0.44 (0.01, 11.78)	2.66 (0.26, 38.71)	4.24 (0.45, 58.34)	9.98* (1.08, 139.70)	0.73 (0.03, 17.95)	6.07 (0.21, 269.50)	1.83 (0.16, 27.09)	1.06 (0.04, 28.28)	2.80 (0.11, 71.27)	6.53 (0.44, 127.90)	—

PUBLICATION BIAS

The standard error of the log odds ratio was plotted against the odds ratio for each of the 13 trials that reported serious adverse events. There appears to be no evidence of publication bias for withdrawals due to adverse events, because the point estimates form an inverted funnel shape, with larger trials (smaller SE) clustered close to the summary odds ratio, and smaller trials (larger SE) more widely distributed on either side of the summary estimate (Figure 4.19).

FIGURE 4.19: FUNNEL PLOT ASSESSING THE POTENTIAL FOR PUBLICATION BIAS — WITHDRAWALS DUE TO ADVERSE EVENTS



INFLUENCE OF FUNDING

Of the 40 trials that reported withdrawals due to adverse events, 13 trials had no industry funding (3, 27, 33, 36, 38, 48, 52, 56, 57, 59, 62, 63, 70). In total, 33 withdrawals due to adverse events were reported in the placebo group ($n = 554$) and 41 were reported in the testosterone group ($n = 562$), giving an odds ratio of 1.24 (95% CI 0.77 to 1.99; $I^2 = 0\%$).

RISK OF BIAS

Of the 40 trials that reported withdrawals due to adverse events, 8 were judged to be at low overall risk of bias (28, 29, 31, 33, 46, 48, 52, 67). In these 8 trials, 22 events were reported in the placebo arm (n = 524), and 46 events were reported in the testosterone arms (n = 740), giving an odds ratio of 1.18 (95% CI 0.43 to 3.23; $I^2 = 39\%$).

ERYTHROCYTOSIS

Of the included RCTs, erythrocytosis was reported in 3 trials (42, 49, 70). The type of testosterone therapy used was intramuscular testosterone enanthate in 2 cases (49, 70) and testosterone undecanoate (1000 mg/12 wk) in 1 case (42). In the trial by Aversa and colleagues (43), which involved men with metabolic syndrome or diabetes (mean age 58 yr), 3 patients in the testosterone undecanoate group experienced mild erythrocytosis (n = 40), with no cases reported in the placebo group (n = 10). In the study by Marks and colleagues (49), which involved patients with symptoms of late-onset hypogonadism (mean age 69 yr), 1 patient in the testosterone enanthate group experienced erythrocytosis (n = 22), with no cases in the placebo group (n = 22). In the third study (70), the authors advised that none of the 5 patients with Alzheimer's disease assigned to either of the 2 study groups (placebo or intramuscular testosterone enanthate) developed "polycythemia or hyperlipidemia."

DIABETES

No trials reported newly diagnosed diabetes during the treatment period.

HEART DISEASE

Two trials reported newly diagnosed heart disease during the treatment period (44, 45). Kenny and colleagues (44) enrolled men aged 60 and older with low bone mineral density and physical frailty. Of the 131 participants (mean 77.9 yr) randomized to receive Androgel 1% (5 mg/d), 2 developed heart disease, while 4 cases developed among the 62 men in the placebo group (mean 76.3 yr). In the trial by Sih and colleagues (45), which involved community-dwelling healthy men (mean 65 yr), 1 patient in the intramuscular testosterone cypionate group (200 mg/2 wk; n = 17) developed uncontrolled atrial fibrillation with congestive heart failure. No cases were reported in the placebo group (n = 15; mean 68 yr).

SKIN REACTIONS

Of the included RCTs, 18 reported treatment-related skin reactions (3, 29, 30, 32, 35, 39, 40, 48, 50, 51, 53, 54, 60, 61, 65, 69, 71, 72) (Table 4.20). Events were reported for all routes of administration except pellets. Reactions were most commonly associated with topical (patch or gel) products. Reactions following intramuscular injection were reported by 4 trials (39, 40, 51, 53), and reactions after oral administration was reported by only 1 trial (48).

Overall, skin-related adverse effects ranged from mild skin irritation to rashes and from allergic contact dermatitis and moderate skin erythema to intense edema and blistering (Table 4.20). Three trials reported that patients experienced blistering as a result of testosterone treatment. Of these, 2 were associated with testosterone patches and 1 was associated with the application of testosterone gel to the skin. In most trials, at least some of the participants who experienced a reaction discontinued treatment; however, it was unclear for a number of trials whether the affected participants withdrew following the reported skin reaction.

TABLE 4.20: REPORTED SKIN REACTIONS IN RANDOMIZED CONTROLLED TRIALS

Trial	Group description (no. randomized)	No. of reported skin reactions	Did the affected participant withdraw from the study as a result of skin-related adverse drug events?	Comments
Ho 2012	• Placebo (60) • IM TU 1000 mg/12 wk (60)	• Placebo: 0 • IM TU: 2	No	Participants reported having acne on the face and body
Kaufman 2011	• Placebo (40) • Gel 1.62%, 40.5 mg/d (234)	• Placebo: 2 • Gel 1.62%: 16	Unclear: skin reactions were described as “treatment emergent adverse events”; however, whether they discontinued the trial was not reported	Reported as “skin and subcutaneous tissue disorders. 5 of the 16 participants with skin disorders in the testosterone group experienced contact dermatitis
Jones 2011	• Placebo (112) • Gel 2%, 60 mg/d (108)	Pruritus: • Placebo: 4% • Gel: 4% “Skin and subcutaneous tissue disorders” • Placebo: 10 • Gel: 11	Yes: “The most common AEs leading to discontinuation were skin and subcutaneous tissue disorders (21 AEs; testosterone, 11; placebo, 10).”	Unclear whether participants with pruritus also withdrew or if they are included in the number of withdrawals due to skin and subcutaneous disorders
Srinivas-Shankar 2010	• Placebo (136) • Gel 1%, 50 mg/d (138)	• Placebo: 1 • Gel 1%: 3	Yes: 2 of the participants in the gel group with a skin rash discontinued treatment	Skin reaction reported as “skin rash”
Basaria 2010	• Placebo • Gel 1%, 100 mg/d	• Placebo: 8 • Gel 1%: 19	Yes: 8 men withdrew because of reaction to the study gel (not reported as to which group)	Significant difference in skin and subcutaneous tissue disorders between groups
Shores 2009	• Placebo (16)	• Placebo: 0	Yes: 1 participant in the	One man in the testosterone group

Trial	Group description (no. randomized)	No. of reported skin reactions	Did the affected participant withdraw from the study as a result of skin-related adverse drug events?	Comments
	• Gel 1%, 75 mg/d (17)	• Gel 1%: 1	testosterone group withdrew because of "skin irritation from the gel"	experienced "skin irritation"
Chiang 2009	• Placebo (20) • Gel 1%, 50 mg/d (20)	• Placebo: 2 • Gel 1%: 0	Yes: 2 patients in the placebo group were "withdrawn from the study" because of skin-related adverse events	Two men in the placebo group experienced "skin rash and dermatitis"
Emmelot-Vonk 2009	• Placebo (117) • Oral TU, 160 mg/d (120)	• Placebo: 7 • Oral TU: 7	Unclear: List of withdrawals does not explicitly state that patients who experienced "skin problems" withdrew from the trial	A total of 14 men (7 each group) experienced "skin problems" not described
Raynaud 2008	• Patch, 4.8 mg/d (188) • IM TE, 250 mg/3 wk (36)	Patch or injection site reaction • Patch: 43 • IM TE: 2 Erythema and papules were also assessed but data NR by group	Unclear: whether patients who experienced a reaction were withdrawn was not reported	"Scores of 3 (erythema and papules) were observed mainly in the first 3 months of treatment in a few number of patients (5 patients at week 7 and 4 patients at week 14). Only 2 patients at week 27 and 1 patient at week 53 showed erythema and papules, leading to definitive discontinuation of the treatment in one of them. The percentages of patients with no evidence of irritation or with minimal erythema, barely perceptible, increased progressively over time: 85.6, 88.5, 90.9, 95.4% at weeks 7, 14, 27, 53, respectively."
Chiang 2007	• Placebo (20) • Gel 1%, 50 mg/d (20)	• Placebo: 2 • Gel 1%: 0	Unclear: Reporting not clear as to whether participants withdrew because of skin irritations	Two men in the placebo group experienced moderate skin erythema (arms, buttocks, head) and mild skin rash (upper arms)
Brockenbrough 2006	• Placebo (21) • Gel 1%, 100 mg/d (19)	• Placebo: 2 • Gel 1%: 2	Yes: 1 participant from the testosterone group withdrew because of acne	Two men from each group experienced rash and acne, which the authors described as "minor side effects"
Kuhnert 2005	• Patch, 5 mg/d (52) • Gel 2.5%, 125 mg/d (56) • Gel 2.5%, scrotal, 25 mg/d (54)	• Patch: 13 • Gel 2.5%: 2 • Scrotal gel 2.5%: 2	Yes: 6 of the 13 patients with skin reactions in the patch group withdrew	"In the case of the patch application site, irritant reactions, erythema or pruritus were described. In the scrotal gel group, one patient also complained of pruritus after gel application and another of burning at the application site. One patient in the dermal group reported dryness at the application site, and another observed erythema when he did not remove the gel and perspired at the same time."
Schubert 2004	• IM TU 1000 mg/9 wk (20) • IM TE, 250 mg/3 wk (20)	• IM TU: 1 • IM TE: 3	No	One man in each group experienced injection site pain, and 2 men in the IM TE group experienced mild acne or "skin problems (spots)"
Steidle 2003	• Placebo (99) • Gel 1%, 50 mg/d (99) • Gel 1%, 100 mg/d (106) • Patch, 5 mg/d (102)	• Placebo: 6 • Gel 1% (doses not reported separately): 17 • Patch: 37	Yes: 15 patients in the patch group discontinued treatment because of "local dermal site reactions". No patients in the gel groups discontinued treatment because of an adverse skin reaction	Some in each group experienced minimal erythema. Some participants in the patch group experienced minimal erythema, moderate erythema with sharply defined borders, intense erythema with or without edema, and intense erythema with edema and blistering.
McNicholas 2003	• Gel 1%, 50 mg/d (68)	• Gel 1%, 50 mg/d: 5*	Yes: The authors reported that some that discontinued	Some patients in the 50 mg/d gel group experienced minimal erythema or intense

Trial	Group description (no. randomized)	No. of reported skin reactions	Did the affected participant withdraw from the study as a result of skin-related adverse drug events?	Comments
	• Gel 1%, 100 mg/d (72)	• Gel 1%: 100 mg/d: 4*	treatment due to skin reactions, but group assignment was not clear.	erythema with or with no oedema. Some patients in the 100 mg/d gel group experienced minimal erythema and moderate erythema with sharply defined borders
Wang 2000	• Patch, 5 mg/d (76) • Gel 1%, 50 mg/d (73) • Gel 1%, 100 mg/d (78)	• Patch: 14 • Gel 1%: 65.8% of treated participants (data not reported by dose)	Yes: 16 participants in the patch group discontinued treatment because of "skin irritation"	More than half of participants who received patch experienced minimal to severe skin irritation ("mild erythema to intense erythema with blisters"). Participants in the patch group experienced moderate to severe skin reactions at the application site
Dobs 1999	• Patch, 5 mg/d (33) • IM TE, 200 mg/2 wk (33)	• Patch: 17 • IM TE: 1	Yes: 3 patients in the patch group discontinued treatment because of "transient skin irritation" caused by the patch	About 60% of patients in the patch group experienced "mild to moderate erythema or pruritus at an application site at least once during the study". Two patients experienced allergic contact dermatitis at the patch application site. About 33% of patients in the IM TE group experienced "at least one local reaction during the study (e.g., pain or soreness, bruising, erythema, swelling, nodules, or furunculosis)"
Bhasin 1998	• Placebo (21) • Patch, 5 mg/d (20)	• Placebo: 3 • Patch: 6	Unclear: "Three men withdrew in the first 15 days of the treatment period; 6 additional men withdrew before completing 10 weeks of treatment"	Eight men (3 in the placebo group and 5 patch group) "experienced reactions at the application site". One man experienced blister formation as a result of the patch, which the authors stated was "related to rupture of the patch." One man experienced an adverse experience related to "skin and appendages."
Note: IM = intramuscular, *Data extracted from a figure showing the frequency distribution of men with positive skin irritation scores.				

SUBGROUP ANALYSES

In general, limited data were available for most subgroup analyses, and the findings should be interpreted with caution.

ROUTE OF ADMINISTRATION

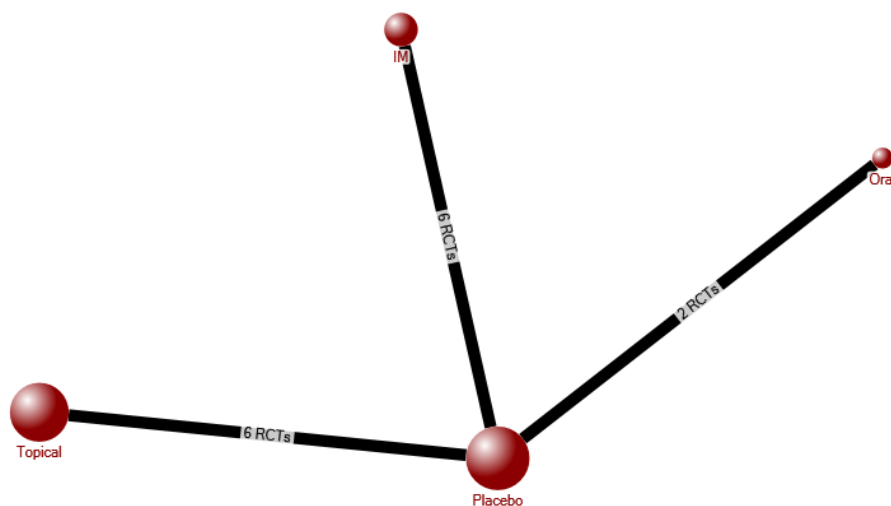
We next questioned whether there was a difference in the odds of a harm outcome (cardiovascular death, myocardial infarction, serious adverse event, withdrawal due to adverse event) depending on the route of testosterone administration.

CARDIOVASCULAR DEATH

Of the trials included in the network for cardiovascular death, 6 involved intramuscular treatments (31, 33, 34, 36, 38, 40), 6 involved topical treatments (3, 26, 29, 30, 32, 35), and 2 involved oral treatments (27, 37). One trial was excluded from this network because both treatments involved intramuscular injection (IM TU 1000 mg/12 wk v. IM TE 250 mg/3wk; (39)).

The network for cardiovascular death by route of administration involved 3 routes (topical, intramuscular, oral) and 2061 participants (Figure 4.20).

FIGURE 4.20: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH BY ROUTE OF ADMINISTRATION



Compared with placebo, there was no increased odds of cardiovascular death associated with any route of administration. Among the treatments, there were no significant differences in the odds of cardiovascular death (Table 4.21). This finding was consistent after an adjusted continuity correction was applied to treatment arms with zero events (Table 4.22).

TABLE 4.21: CARDIOVASCULAR DEATH, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Topical	IM	Oral
Topical	1.34 (0.34, 4.90)	—		
IM	0.34 (0.05, 1.91)	0.26 (0.02, 2.19)	—	
Oral	0.12 (0.00, 4.22)	0.09 (0.00, 4.24)	0.33 (0.00, 22.66)	—

Note: IM = intramuscular.

TABLE 4.22: CARDIOVASCULAR DEATH, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Topical	IM	Oral
Topical	1.33 (0.43, 3.99)	—		
IM	0.61 (0.15, 2.08)	0.46 (0.08, 2.55)	—	
Oral	0.50 (0.03, 4.81)	0.39 (0.02, 4.92)	0.82 (0.04, 11.82)	—

Note: IM = intramuscular.

MYOCARDIAL INFARCTION

Of the trials that reported myocardial infarction, 4 involved treatment with intramuscular testosterone (31, 36, 40, 43) and 5 involved topical testosterone (3, 29, 30, 32, 44). One trial (42) compared both oral and intramuscular injection testosterone to placebo. The network for the risk of myocardial infarction associated with testosterone replacement therapy included 1562 participants and 3 routes of administration (Figure 4.21). Twelve comparisons were made, based on 9 trials with 2 arms and 1 trial with 3 arms.

There were no differences in the odds of myocardial infarction between placebo and any route of administration, and there were no significant differences in the odds between the routes (Table 4.23). This finding was consistent after adjustment for zero event counts in the network (Table 4.24).

FIGURE 4.21: EVIDENCE NETWORK FOR MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION

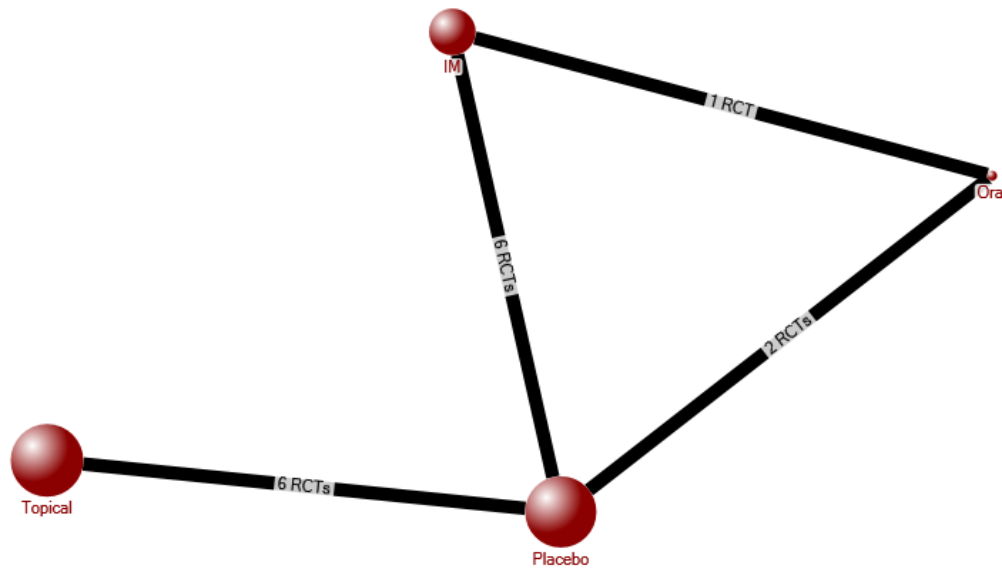


TABLE 4.23: MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Topical	IM	Oral
Topical	0.43 (0.06, 2.13)	—		
IM	0.19 (0.02, 1.01)	0.45 (0.03, 5.41)	—	
Oral	0.05 (0.00, 1.31)	0.12 (0.00, 5.86)	0.27 (0.00, 14.14)	—

Note: IM = intramuscular.

TABLE 4.24: MYOCARDIAL INFARCTION, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Topical	IM	Oral
Topical	0.65 (0.18, 2.25)	—		
IM	0.32 (0.07, 1.28)	0.49 (0.08, 3.24)	—	
Oral	0.22 (0.01, 2.89)	0.33 (0.01, 6.11)	0.66 (0.02, 13.99)	—

Note: IM = intramuscular.

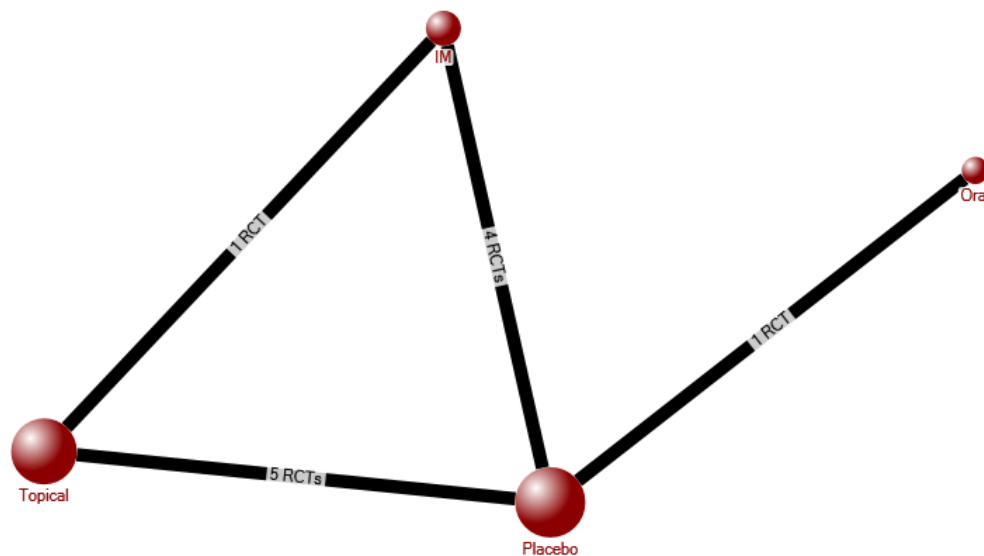
STROKE

There were insufficient data to perform network meta-analysis by route of administration for stroke. In the pairwise meta-analysis (Figure 4.8), there was no significant difference in odds of stroke compared with placebo for intramuscular testosterone (OR 0.12, 95% CI 0.00 to 6.02) or topical testosterone (OR 0.96, 95% CI 0.06 to 15.46) (Figure 4.9). No trials involving oral testosterone reported stroke during the treatment period

PROSTATE CANCER

The network for prostate cancer involved 3 routes of administration. Of the 10 trials in this network, 5 involved topical administration compared with placebo (3, 26, 32, 44, 50), 4 involved intramuscular administration compared with placebo (36, 46, 47, 49), and 1 involved comparison between oral administration and placebo (48). One trial involved comparison of topical and intramuscular routes of administration (51). The network for prostate cancer by route of administration included 2028 participants randomized to 3 routes of administration (Figure 4.22). Eleven comparisons were made, based on 11 trials each comparing 2 routes of administration.

FIGURE 4.22: EVIDENCE NETWORK FOR PROSTATE CANCER, BY ROUTE OF ADMINISTRATION



There was no significant difference in the odds of prostate cancer between placebo and any of the routes of administration, and there were no significant differences among the routes (Table 4.25). This finding was consistent after adjustment for zero cells in the network (Table 4.26).

TABLE 4.25: PROSTATE CANCER, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Topical	IM	Oral
Topical	0.59 (0.14, 2.17)	—		
IM	0.57 (0.16, 1.89)	0.97 (0.19, 4.80)	—	
Oral	0.06 (0.00, 1.58)	0.11 (0.00, 3.93)	0.11 (0.00, 3.70)	—

Note: IM = intramuscular.

TABLE 4.26: PROSTATE CANCER, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

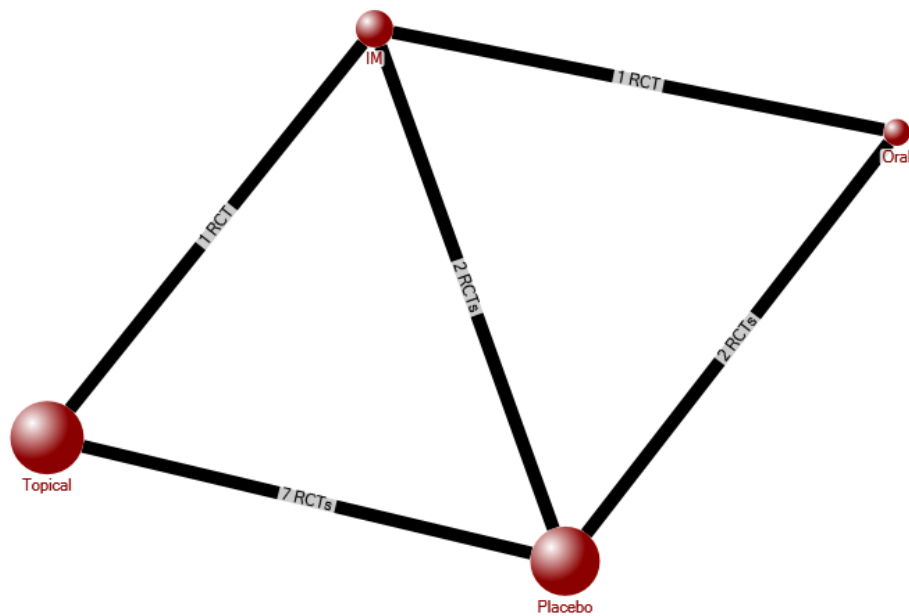
	Placebo	Topical	IM	Oral
Topical	0.70 (0.20, 2.32)	—		
IM	0.65 (0.21, 2.05)	0.95 (0.22, 4.02)	—	
Oral	0.17 (0.01, 1.86)	0.23 (0.01, 3.72)	0.25 (0.01, 3.72)	—

Note: IM = intramuscular.

SERIOUS ADVERSE EVENTS

Of the 13 trials that reported serious adverse events during the treatment period, 12 were included in the network investigating the odds of a serious adverse event by route of administration. One trial was excluded from this network because both trial arms involved intramuscular injection (39). Of the included trials, 7 involved a comparison between a topical testosterone product and placebo, 2 compared an intramuscular product and placebo, and 1 compared an oral product and placebo. One trial compared topical and intramuscular products, and 1 trial compared placebo, oral, and intramuscular products (3 arms). The network for route of administration involved 2144 people, and 14 comparisons based on 11 trials with 2 arms and 1 trial with 3 arms (Figure 4.23).

FIGURE 4.23: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION



There was no significant difference in the odds of a serious adverse event between placebo and any of the routes of administration, and there were no significant differences among the routes (Table 4.27). This finding was consistent after adjustment for zero cells in the network (Table 4.28).

TABLE 4.27: SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Topical	IM	Oral
Topical	1.15 (0.61, 2.14)	—		
IM	0.60 (0.19, 1.64)	0.52 (0.15, 1.58)	—	
Oral	0.43 (0.11, 1.58)	0.38 (0.09, 1.64)	0.73 (0.13, 4.02)	—

Note: IM = intramuscular.

TABLE 4.28: SERIOUS ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Topical	IM	Oral
Topical	1.16 (0.62, 2.12)	—		
IM	0.63 (0.20, 1.73)	0.54 (0.16, 1.63)	—	
Oral	0.45 (0.12, 1.54)	0.38 (0.09, 1.56)	0.72 (0.13, 3.78)	—

Note: IM = intramuscular.

WITHDRAWALS DUE TO ADVERSE EVENTS

Of the 40 RCTs that reported withdrawals due to adverse events during the treatment period, 15 involved comparison between a topical testosterone and placebo, 17 involved comparison between intramuscular testosterone and placebo, and 5 involved comparison between an oral product and placebo. One trial involved comparison between topical and intramuscular testosterone. Two trials were excluded from this analysis because both treatment arms involved the same route of administration (39, 65).

The network for withdrawals due to adverse events by route of administration included 3586 participants randomized to 3 routes of administration (Figure 4.24). The network comprised 38 comparisons based on 38 trials with 2 arms each.

There was no significant difference in the odds of a withdrawal due to an adverse event between placebo and any route of administration, and there were no significant differences between the routes (Table 4.29). Adjustment for zero event counts in the network did not alter the significance of any point estimate (Table 4.30).

FIGURE 4.24: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION

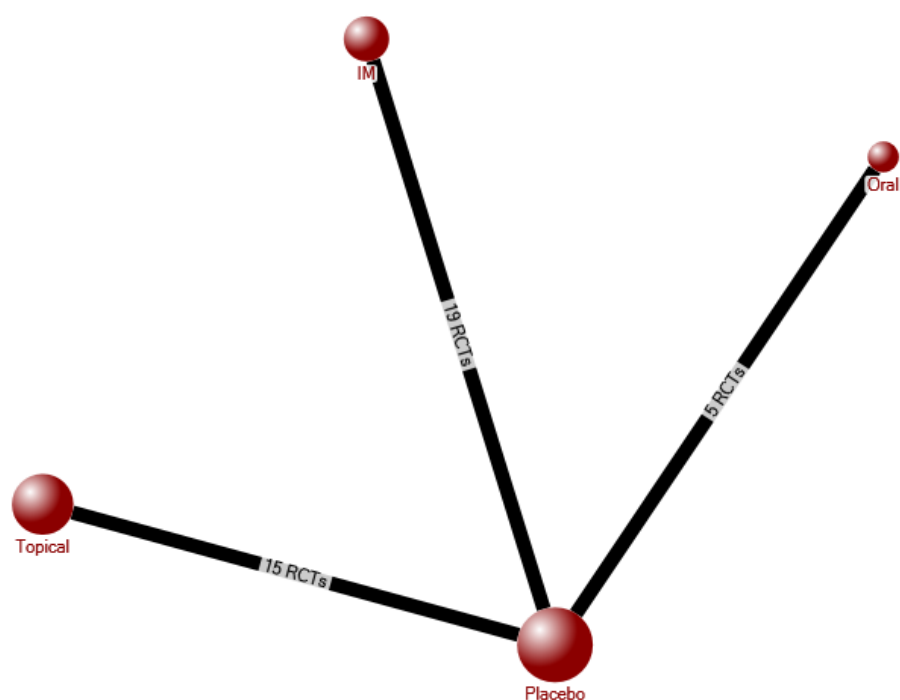


TABLE 4.29: WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), BY ROUTE

	Placebo	Topical	IM	Oral
Topical	1.13 (0.72, 1.78)	—		
IM	1.14 (0.60, 2.10)	1.01 (0.47, 2.13)	—	
Oral	0.86 (0.28, 2.59)	0.77 (0.23, 2.47)	0.76 (0.22, 2.67)	—

Note: IM = intramuscular.

TABLE 4.30: WITHDRAWALS DUE TO ADVERSE EVENTS, BY ROUTE OF ADMINISTRATION — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Topical	IM	Oral
Topical	1.13 (0.77, 1.71)	—		
IM	1.18 (0.67, 2.07)	1.04 (0.52, 2.03)	—	
Oral	0.96 (0.39, 2.32)	0.84 (0.32, 2.22)	0.82 (0.28, 2.35)	—

Note: IM = intramuscular.

DURATION OF TREATMENT

CARDIOVASCULAR DEATH

LESS THAN 6 MONTHS

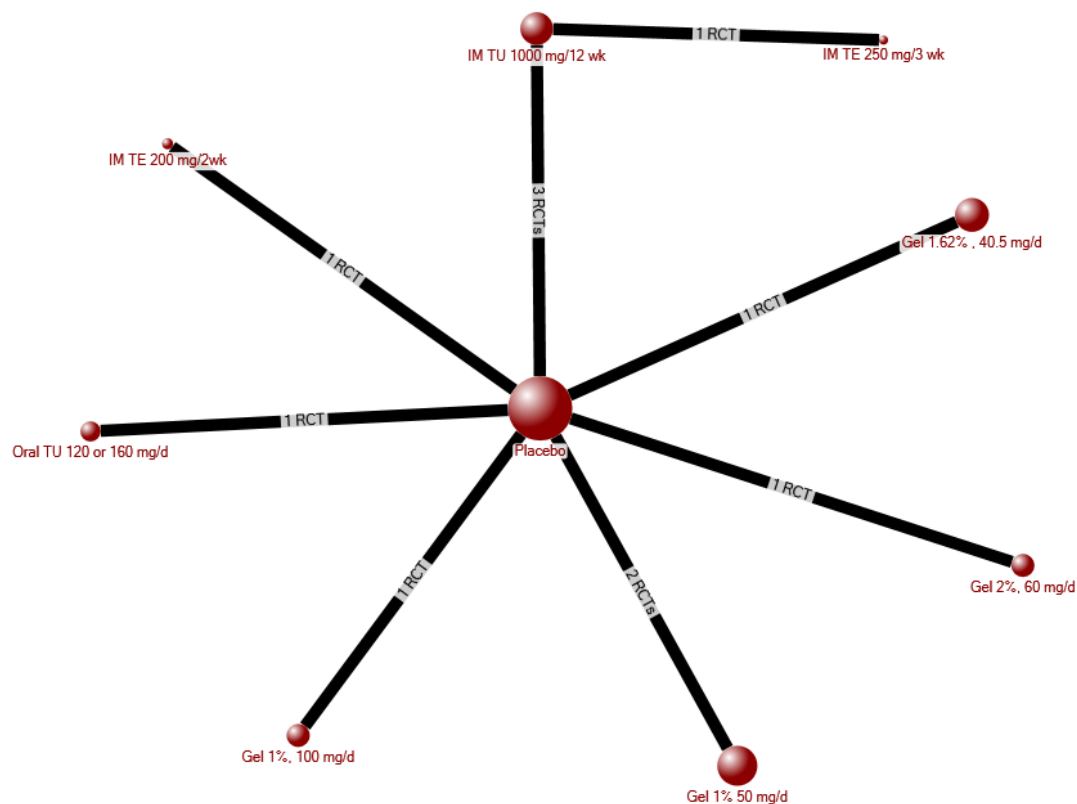
Of the 15 trials that reported cardiovascular death during the treatment period, only 4 involved treatment for under 6 months (33, 35, 37, 38, 73). Caminiti and colleagues (33), Boyanov and colleagues (37), and Clague and colleagues (38) all reported no cardiovascular death in either treatment or control group, while Brockenbrough and colleagues (35) reported 3 cardiovascular deaths in the testosterone gel group (50 mg/d, n = 19) and none in the placebo group (n = 21), giving an odds ratio of 9.20 (95% CI 0.90 to 94.21). The data were insufficient to perform network meta-analysis to assess the odds of cardiovascular death associated with individual testosterone treatments.

SIX MONTHS OR LONGER

Eleven trials with a treatment period of 6 months or longer reported cardiovascular death (3, 26, 27, 29-32, 34, 36, 39, 40). Of these, 10 involved comparison between testosterone and placebo. Among these trials, 5 cardiovascular deaths were reported in the testosterone group (n = 1065), and 3 cardiovascular deaths were reported in the placebo group (n = 824), giving an odds ratio of 1.56 (95% CI 0.39 to 6.27; $I^2 = 2\%$). Zero cardiovascular deaths were reported in either arm of the one head-to-head trial of intramuscular testosterone undecanoate (1000 mg/9 wk) versus intramuscular testosterone enanthate (250 mg/3 wk) (39).

The network for cardiovascular deaths associated with the use of testosterone replacement products included 11 trials and a total of 1929 participants. Five trials had a duration of 6 months (3, 26, 27, 29, 32), 5 had a duration of between 6 months and 1 year (30, 31, 34, 39, 40), and 1 had a duration of 3 years (36). Eight treatments were compared in the network, giving 11 comparisons based on 11 trials each with 2 arms (Figure 4.25).

FIGURE 4.25: EVIDENCE NETWORK FOR CARDIOVASCULAR DEATH AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER



Compared with placebo, there were no significant differences in the odds of cardiovascular death (Table 4.31). In the head-to-head comparison, there were no significant differences between the treatments.

TABLE 4.31: CARDIOVASCULAR DEATH, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL), CONTINUITY CORRECTION

	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 or 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk
Gel 1%, 50 mg/d	1.45 (0.23, 10.50)	—							
Gel 1%, 100 mg/d	1.49 (0.11, 23.29)	1.01 (0.04, 29.96)	—						
Gel 1.62%, 40.5 mg/d	0.35 (0.01, 10.86)	0.24 (0.01, 11.70)	0.25 (0.00, 16.16)	—					
Gel 2%, 60 mg/d	0.25 (0.01, 3.50)	0.16 (0.00, 4.73)	0.16 (0.00, 8.09)	0.67 (0.01, 41.61)	—				
Oral TU 120 or 160 mg/d	0.50 (0.01, 10.76)	0.34 (0.01, 12.25)	0.33 (0.00, 18.92)	1.40 (0.01, 146.80)	2.22 (0.02, 178.90)	—			
IM TU, 1000 mg/12 wk	0.69 (0.14, 3.19)	0.47 (0.04, 5.20)	0.47 (0.02, 9.58)	1.98 (0.04, 71.50)	2.87 (0.12, 126.00)	1.34 (0.04, 81.75)	—		
IM TE, 200 mg/2 wk	0.58 (0.01, 15.04)	0.39 (0.01, 16.71)	0.38 (0.00, 22.36)	1.54 (0.01, 178.30)	2.36 (0.02, 298.70)	1.18 (0.01, 127.10)	0.82 (0.01, 30.93)	—	
IM TE, 250 mg/3 wk	0.43 (0.01, 12.92)	0.29 (0.00, 14.26)	0.28 (0.00, 21.56)	1.22 (0.01, 128.50)	1.81 (0.02, 222.90)	0.83 (0.01, 129.40)	0.63 (0.02, 15.34)	0.76 (0.00, 109.00)	—
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.									

MYOCARDIAL INFARCTION

All 10 trials that reported myocardial infarction had a treatment duration of 6 months or longer. Four trials had a duration of 6 months (3, 29, 32, 42), 4 had a duration between 6 months and 1 year (30, 31, 40, 43), 1 had a duration of 2 years (44) and 1 had a duration of 3 years (36). In total, 5 events were reported in the testosterone group ($n = 902$), and 7 events were reported in the placebo group ($n = 628$), giving an overall odds ratio of OR 0.45 (95% CI 0.14 to 1.50; $I^2 = 41\%$). In the network meta-analysis, there was no significant difference in the odds of cardiovascular death between placebo and any testosterone treatment, and there were no significant differences among the treatments (Table 4.8).

STROKE

LESS THAN 6 MONTHS

Of the 4 trials that reported stroke, 1 had a treatment duration of less than 6 months (35). Brockenbrough and colleagues reported 1 stroke in the placebo group ($n = 21$), and zero events in the testosterone gel group (1%, 50 mg/d), giving an odds ratio of 0.15 (95% CI 0.00 to 7.54).

SIX MONTHS OR LONGER

Three trials involved a treatment duration of 6 months or longer (3, 36, 45). One with a duration of 6 months (3), 1 with a duration of 1 year (45), 1 with a duration of 3 years. Overall, 1 event was reported in each group (testosterone $n = 191$; placebo $n = 142$), giving an overall odds ratio of 1.08 (95% CI 0.07 to 17.32). Network meta-analysis was not possible for this outcome because of limited data.

PROSTATE CANCER

LESS THAN 6 MONTHS

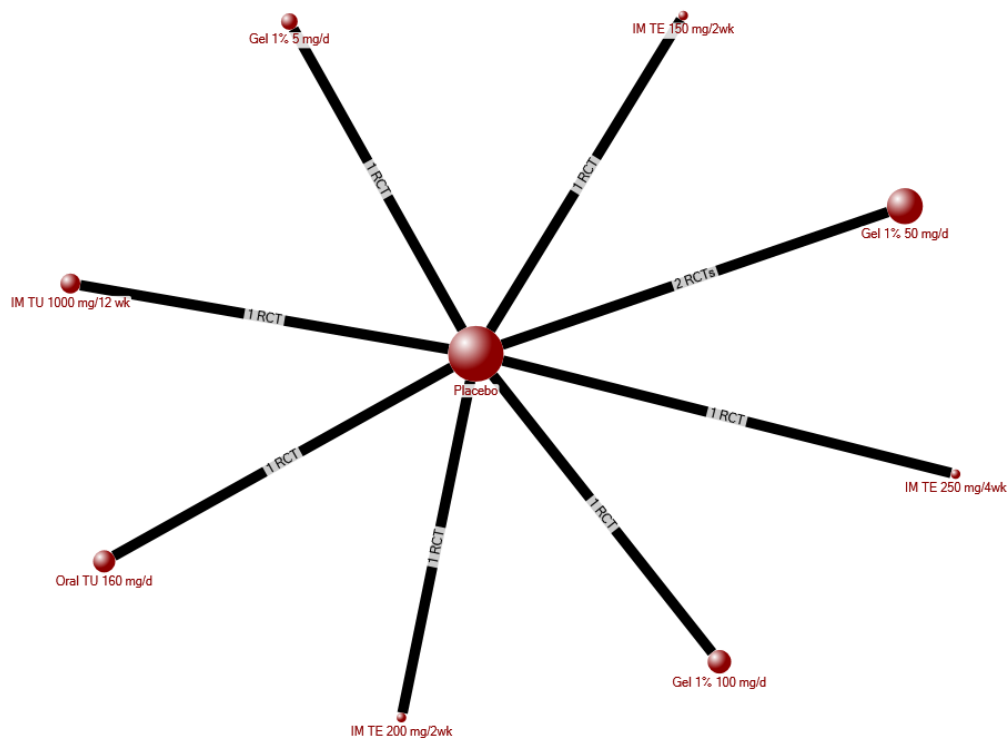
Of the 11 trials that reported prostate cancer during the treatment period, 2 involved a treatment duration of less than 6 months (50, 51). In the trial by Dobs and colleagues (51), 1 case of prostate cancer was reported in the patch group (5 mg/d, $n = 33$) and 2 cases were reported in the intramuscular testosterone enanthate group (200 mg/2 wk, $n = 33$). In the 4-arm trial by Steidle and colleagues, zero events were reported in the placebo group ($n = 99$), 50 mg/d gel group ($n = 99$), and 100 mg/d gel group ($n = 106$); 2 events were reported in the patch group (5 mg/d, $n = 102$). Network meta-analysis was not possible for this outcome because of limited data.

SIX MONTHS OR LONGER

Nine trials that reported prostate cancer involved a treatment duration of 6 months or longer: 4 had a duration of 6 months (3, 26, 32, 49), 3 had a duration between 6 months and 1 year (44, 46-48), 1 had a duration of 2 years (44), and 1 had a duration of 3 years (36). Overall, 7 events were reported in the testosterone group ($n = 785$), and 10 events were reported in the placebo group ($n = 771$), giving an overall odds ratio of 1.48 (95% CI 0.56 to 3.91; $I^2 = 0\%$).

The network for prostate cancer among trials with a treatment duration of 6 months or longer involved 8 treatments and a total of 1563 participants. Nine direct comparisons were included, based on 9 trials each with 2 arms (Figure 4.26).

FIGURE 4.26: EVIDENCE NETWORK FOR PROSTATE CANCER AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER



There were no significant differences in the odds of prostate cancer between placebo and any testosterone replacement therapy included in the network, and there were no significant differences among the treatments (Table 4.32).

TABLE 4.32: PROSTATE CANCER, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 150 mg/2wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/ 4 wk
Gel 1%, 5 mg/d	0.61 (0.03, 8.64)	—							
Gel 1%, 50 mg/d	0.63 (0.07, 4.07)	1.02 (0.04, 33.49)	—						
Gel 1%, 100 mg/d	1.46 (0.10, 24.72)	2.42 (0.06, 140.90)	2.36 (0.10, 71.99)	—					
Oral TU 160 mg/d	0.17 (0.00, 1.97)	0.27 (0.00, 13.67)	0.25 (0.01, 7.14)	0.11 (0.00, 4.64)	—				
IM TU, 1000 mg/12 wk	0.27 (0.01, 4.19)	0.42 (0.00, 26.06)	0.42 (0.01, 13.09)	0.17 (0.00, 8.49)	1.74 (0.02, 125.60)	—			
IM TE, 150 mg/2wk	0.41 (0.05, 2.85)	0.66 (0.02, 21.03)	0.64 (0.04, 11.27)	0.27 (0.01, 7.46)	2.44 (0.09, 146.70)	1.51 (0.05, 86.89)	—		
IM TE, 200 mg/2 wk	1.60 (0.14, 20.43)	2.72 (0.07, 121.80)	2.58 (0.12, 67.79)	1.07 (0.03, 44.37)	10.06 (0.25, 855.80)	6.21 (0.15, 510.50)	4.01 (0.16, 117.00)	—	
IM TE, 250 mg/4 w	0.59 (0.01, 14.32)	0.93 (0.01, 78.30)	0.93 (0.01, 40.53)	0.38 (0.00, 27.49)	3.60 (0.03, 379.10)	2.16 (0.02, 282.30)	1.44 (0.02, 70.26)	0.35 (0.00, 21.02)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

SERIOUS ADVERSE EVENTS

LESS THAN 6 MONTHS

Of the 13 trials that reported serious adverse events during the treatment period, 3 had a treatment duration of less than 6 months (52, 54, 55). All 3 trials involved topical testosterone products compared to placebo. Four events were reported in the testosterone group (n = 96), and 4 events were reported in the placebo group (n = 97), giving an odds ratio of 0.99 (95% CI 0.24 to 4.05; $I^2 = 27\%$).

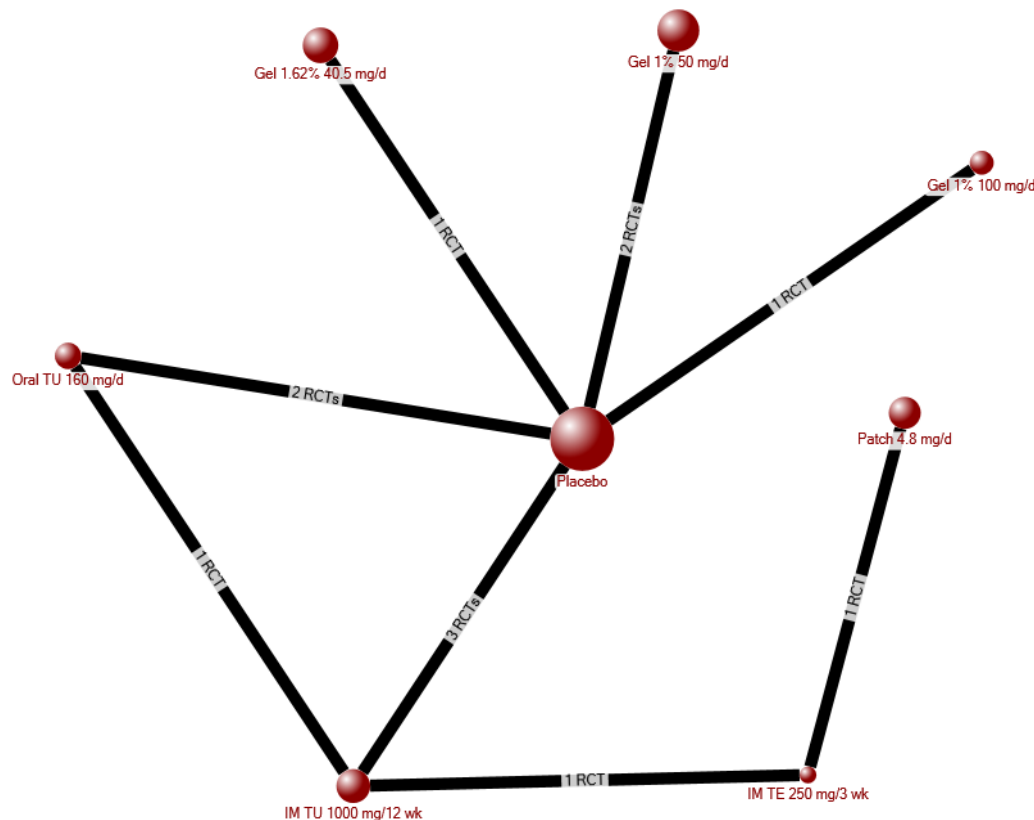
SIX MONTHS OR LONGER

Ten trials with a treatment duration of 6 months or longer reported serious adverse events: 6 involved a treatment duration of 6 months (3, 26, 29, 32, 42, 48), and 4 involved treatment durations of up to 1 year (39, 40, 46, 53). Eight trials involved comparison between a testosterone product and placebo, and 2 involved head-to-head comparisons of testosterone products. Among the placebo controlled trials, 42 events were reported in the testosterone groups (n = 980) and 36 events were reported in the placebo group (n = 747), giving an odds ratio of 1.01 (95% CI 0.57 to 1.79, $I^2 = 21\%$). In the head-to-head trial between intramuscular undecanoate (1000 mg/12 wk, n = 20) and intramuscular testosterone

enanthate (250 mg/3 wk, n = 20), no serious adverse events were reported in either group (39). In the head-to-head trial by Raynaud and colleagues (53), 9 serious adverse events were reported in the patch group (4.8 mg/d, n = 188) and 3 events were reported in the intramuscular testosterone enanthate group (250 mg/3 wk, n = 36).

The network for serious adverse events among trials with a treatment duration of 6 months or longer involved 8 treatments and 1991 participants. The network comprised 12 comparisons, based on 9 trials with 2 arms and 1 trial with 3 arms (Figure 4.27).

FIGURE 4.27: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER



There were no significant differences in the odds of a serious adverse event between any of the testosterone replacement therapies and placebo, and there were no significant differences among the treatments (Table 4.33).

TABLE 4.33: SERIOUS ADVERSE EVENTS, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch, 4.8 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 250 mg/ 3 wk
Patch, 4.8 mg/d	0.29 (0.01, 7.30)	—						
Gel 1%, 50 mg/d	1.31 (0.49, 3.69)	4.48 (0.16, 127.10)	—					
Gel 1%, 100 mg/d	2.07 (0.64, 6.70)	7.11 (0.23, 206.90)	1.58 (0.32, 7.26)	—				
Gel 1.62%, 40.5 mg/d	0.74 (0.12, 7.00)	2.74 (0.06, 118.10)	0.57 (0.07, 6.39)	0.36 (0.04, 4.46)	—			
Oral TU 160 mg/d	0.44 (0.11, 1.52)	1.48 (0.05, 44.39)	0.33 (0.06, 1.63)	0.21 (0.04, 1.19)	0.58 (0.04, 5.55)	—		
IM TU, 1000 mg/12 wk	0.39 (0.10, 1.37)	1.28 (0.06, 31.88)	0.29 (0.05, 1.43)	0.19 (0.03, 1.04)	0.50 (0.04, 4.67)	0.87 (0.14, 5.27)	—	
IM TE, 250 mg/3 wk	0.42 (0.02, 8.65)	1.48 (0.26, 6.80)	0.32 (0.01, 7.49)	0.20 (0.01, 5.17)	0.54 (0.01, 20.13)	1.00 (0.04, 23.45)	1.12 (0.06, 20.83)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

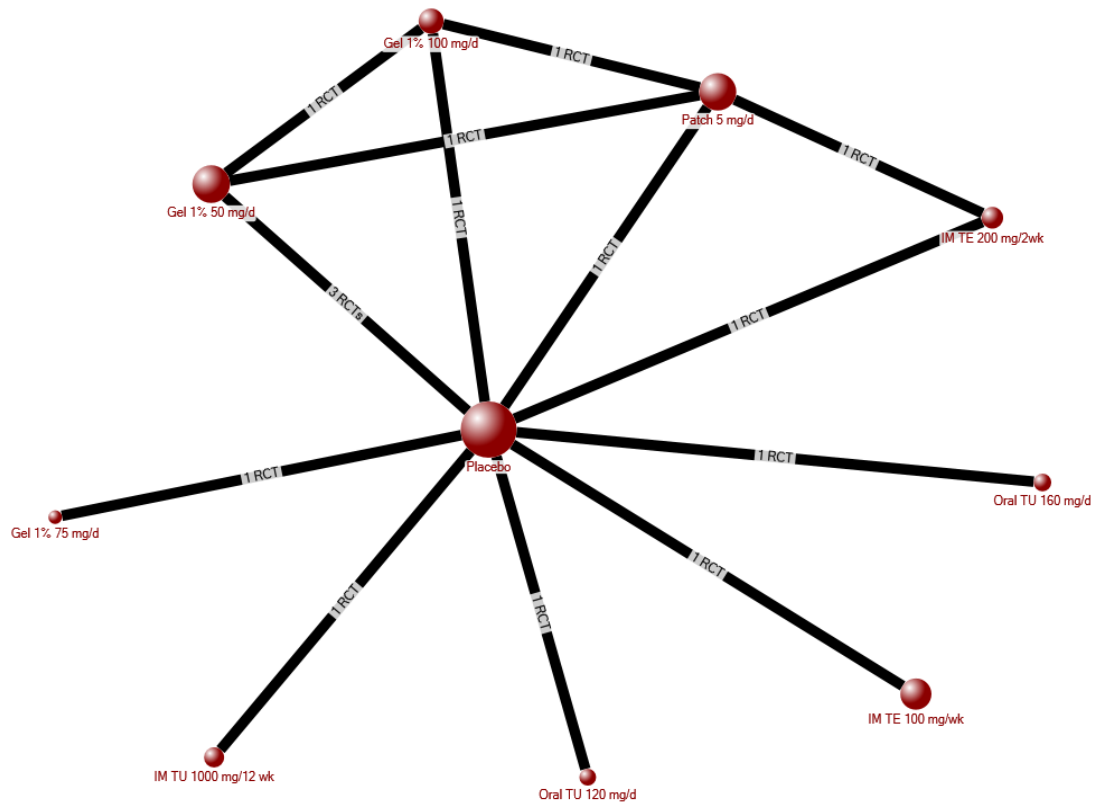
WITHDRAWALS DUE TO ADVERSE EVENTS

LESS THAN 6 MONTHS

Of the 40 trials that reported withdrawals due to adverse events, 13 involved a treatment duration of less than 6 months (33, 35, 37, 38, 51, 52, 54, 57, 60, 61, 65, 67, 69). Eleven trials involved comparison between a testosterone product and placebo, with 18 events reported in the testosterone group ($n = 278$) and 10 events reported in the placebo group ($n = 277$), giving an odds ratio of 2.01 (95% CI 0.60 to 6.69; $I^2 = 35\%$). In the 2-arm head-to-head trial by Dobs and colleagues (51), 1 withdrawal due to adverse events was reported in the intramuscular testosterone enanthate group (200 mg/2 wk; $n = 33$) and withdrawals were reported in the patch group (5 mg/d; $n = 33$). In the 3-arm head-to-head trial by McNicholas and colleagues (65), 9 withdrawals due to adverse events were reported in the patch (5 mg/d; $n = 68$), 3 withdrawals were reported in the 50 mg/d gel group ($n = 68$), and zero withdrawals were reported in the 100 mg/d gel group ($n = 72$).

The evidence network for withdrawals due to adverse events among trials with a treatment duration of less than 6 months included 13 studies with a total 796 participants. The network comprised 9 treatments in 12 two-arm trials and 1 three-arm trial, giving a total of 15 direct comparisons (Figure 4.28).

FIGURE 4.28: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION LESS THAN 6 MONTHS



There were no significant differences in the odds of withdrawal due to adverse events between placebo and any of the testosterone replacement therapies, and there were no significant differences among the treatments (Table 4.34).

TABLE 4.34: WITHDRAWALS DUE TO ADVERSE EVENTS, TREATMENT DURATION LESS THAN 6 MONTHS — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 200 mg/ 2 wk
Patch, 5 mg/d	3.42 (0.54, 18.50)	—								
Gel 1%, 50 mg/d	0.91 (0.25, 3.01)	0.27 (0.05, 1.68)	—							
Gel 1%, 75 mg/d	3.40 (0.27, 51.69)	1.00 (0.05, 26.46)	3.76 (0.23, 79.09)	—						
Gel 1%, 100 mg/d	0.78 (0.11, 4.02)	0.23 (0.03, 1.71)	0.85 (0.11, 5.57)	0.22 (0.01, 4.57)	—					
Oral TU 120 mg/d	0.53 (0.01, 17.84)	0.15 (0.00, 8.66)	0.58 (0.01, 25.06)	0.15 (0.00, 13.54)	0.70 (0.01, 40.06)	—				
Oral TU 160 mg/d	3.00 (0.19, 59.70)	0.89 (0.04, 29.95)	3.33 (0.17, 89.28)	0.89 (0.02, 47.57)	3.96 (0.16, 148.30)	5.89 (0.07, 791.50)	—			
IM TU, 1000 mg/12 wk	0.56 (0.01, 17.21)	0.16 (0.00, 7.86)	0.60 (0.01, 25.26)	0.15 (0.00, 12.34)	0.71 (0.01, 38.23)	0.99 (0.00, 212.40)	0.18 (0.00, 13.64)	—		
IM TE, 100 mg/wk	0.56 (0.01, 18.09)	0.16 (0.00, 8.37)	0.62 (0.01, 24.98)	0.16 (0.00, 12.51)	0.75 (0.01, 36.96)	1.07 (0.01, 195.70)	0.18 (0.00, 15.17)	1.08 (0.01, 176.80)	—	
IM TE, 200 mg/2 wk	2.23 (0.15, 27.83)	0.66 (0.05, 8.46)	2.43 (0.15, 37.00)	0.64 (0.01, 21.48)	2.93 (0.15, 58.47)	4.31 (0.05, 414.70)	0.73 (0.01, 30.61)	4.11 (0.05, 468.60)	4.03 (0.05, 414.60)	—

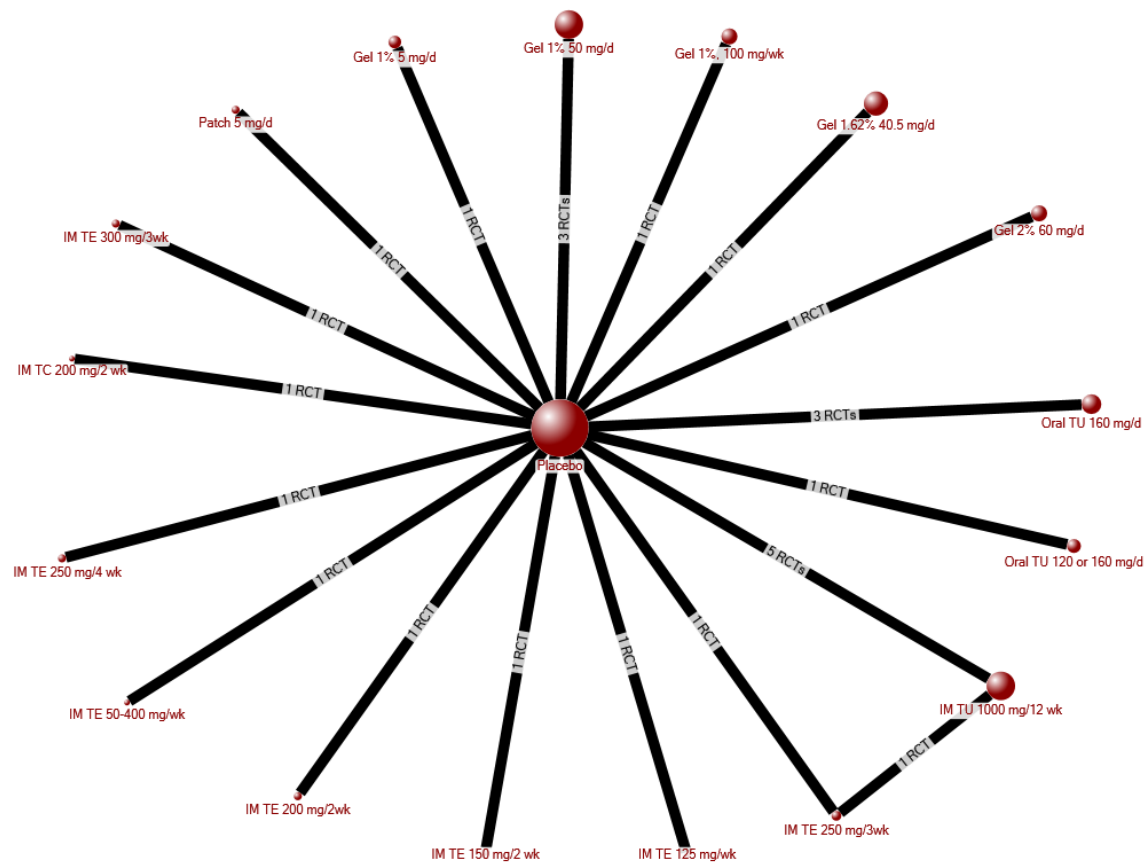
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.

SIX MONTHS OR LONGER

Twenty-six trials involved a treatment duration of 6 months or longer: 11 involved treatment for 6 months (3, 26, 27, 29, 32, 48, 49, 59, 62, 63, 66), 12 involved treatment for between 6 months and 1 year (30, 31, 34, 39, 43, 45-47, 56, 58, 64, 70), 1 involved treatment for 2 years (44), and 1 involved treatment for 3 years (36). Twenty-five trials involved comparison between a testosterone product and placebo, with 143 events reported in the testosterone group (n = 1610) and 106 events reported in the placebo group (n = 1353), giving an odds ratio of 0.93 (95% CI 0.69 to 1.25; $I^2 = 0\%$). In the head-to-head trial by Schubert and colleagues (39), zero events were reported in the intramuscular testosterone undecanoate group (1000 mg/12 wk; n = 20), and 1 event was reported in the intramuscular testosterone enanthate group (250 mg/3 wk; n = 20).

The network for withdrawals due to adverse events among trials with a treatment duration of 6 months or longer included 26 studies with a total of 2963 participants. The network comprised 17 treatments, and included 26 comparisons based on 26 trials with 2 arms each (Figure 4.29)

FIGURE 4.29: EVIDENCE NETWORK FOR WITHDRAWALS DUE TO ADVERSE EVENTS AMONG TRIALS WITH A TREATMENT DURATION OF 6 MONTHS OR LONGER



Compared with placebo, 1.62% testosterone gel (40.5 mg/d) was associated with a significantly higher odds of withdrawal due to adverse events (Table 4.35). There were no significant differences for any other testosterone treatment compared with placebo. In the head-to-head comparison, 1.62% testosterone gel (40.5 mg/d) was associated with a higher odds of withdrawal due to adverse events compared to patch (5 mg/d), 1% testosterone gel (5 mg/d, 50 mg/d, 100 mg/d), oral testosterone undecanoate (160 mg/d) and intramuscular testosterone undecanoate (1000 mg/12 wk). Intramuscular testosterone cypionate (200 mg/2 wk) was associated with an increased odds of withdrawal due to adverse events compared to intramuscular testosterone undecanoate (1000 mg/12 wk). Several of the estimates were associated with wide credible intervals, likely owing to a lack of data for many of the treatments included in the network.

TABLE 4.35: WITHDRAWALS DUE TO ADVERSE EVENTS, TREATMENT DURATION 6 MONTHS OR LONGER — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/wk	IM TE, 150 mg/2 wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/3 wk	IM TE, 250 mg/4 wk	IM TE, 300 mg/3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	0.25 (0.01, 3.68)	—																
Gel 1%, 5 mg/d	0.76 (0.28, 1.99)	3.05 (0.17, 111.10)	—															
Gel 1%, 50 mg/d	0.89 (0.41, 1.90)	3.56 (0.22, 120.50)	1.18 (0.34, 4.06)	—														
Gel 1%, 100 mg/d	0.89 (0.31, 2.52)	3.58 (0.19, 136.10)	1.17 (0.28, 4.94)	1.01 (0.27, 3.64)	—													
Gel 1.62%, 40.5 mg/d	8.59 (1.29, 134.20)	37.35 (1.22, 2493.00)	11.49 (200.30)	9.73 (1.26, 160.90)	9.86 (1.10, 175.60)	—												
Gel 2%, 60 mg/d	1.62 (0.58, 4.61)	6.51 (0.36, 247.20)	2.15 (0.52, 8.98)	1.84 (0.51, 6.67)	1.84 (0.42, 8.24)	0.19 (0.01, 1.65)	—											
Oral TU 160 mg/d	0.84 (0.29, 2.35)	3.34 (0.18, 118.60)	1.10 (0.26, 4.53)	0.94 (0.25, 3.46)	0.94 (0.20, 4.23)	0.10 (0.01, 0.83)	0.51 (0.11, 2.24)	—										
Oral TU 120- 160 mg/d	0.53 (0.01, 12.28)	2.07 (0.03, 212.10)	0.71 (0.01, 19.63)	0.60 (0.01, 16.04)	0.61 (0.01, 16.76)	0.05 (0.00, 2.49)	0.32 (0.01, 9.15)	0.64 (0.01, 18.46)	—									
IM TU, 1000 mg/12 wk	0.49 (0.18, 1.30)	1.99 (0.11, 70.73)	0.65 (0.16, 2.60)	0.55 (0.16, 1.90)	0.55 (0.13, 2.37)	0.06 (0.00, 0.47)	0.30 (0.07, 1.27)	0.59 (0.14, 2.46)	0.92 (0.03, 42.33)	—								
IM TE, 125 mg/wk	6.38 (0.86, 57.20)	25.95 (0.86, 1460.00)	8.48 (0.89, 93.51)	7.20 (0.82, 73.89)	7.17 (0.75, 81.81)	0.74 (0.02, 13.90)	3.93 (0.40, 43.28)	7.75 (0.81, 86.07)	12.63 (0.28, 785.90)	13.21 (1.35, 148.00)	—							
IM TE, 150 mg/2 wk	0.79 (0.04, 10.60)	3.12 (0.06, 245.60)	1.05 (0.05, 16.85)	0.89 (0.05, 13.11)	0.91 (0.04, 14.61)	0.08 (0.00, 2.24)	0.49 (0.02, 7.70)	0.95 (0.04, 15.09)	1.45 (0.02, 132.60)	1.62 (0.08, 25.01)	0.12 (0.00, 3.32)	—						

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/wk	IM TE, 150 mg/2 wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/3 wk	IM TE, 250 mg/4 wk	IM TE, 300 mg/3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/2 wk
IM TE, 200 mg/2 wk	2.61 (0.58, 13.71)	10.54 (0.45, 457.30)	3.45 (0.57, 23.52)	2.94 (0.53, 18.41)	2.96 (0.46, 21.06)	0.30 (0.01, 3.85)	1.60 (0.26, 11.41)	3.15 (0.50, 21.53)	4.91 (0.15, 293.90)	5.36 (0.87, 35.65)	0.41 (0.03, 5.66)	3.29 (0.17, 89.26)	—					
IM TE, 250 mg/3 wk	1.95 (0.30, 13.79)	7.94 (0.30, 377.00)	2.56 (0.31, 23.11)	2.20 (0.30, 17.34)	2.23 (0.25, 20.18)	0.22 (0.01, 3.65)	1.19 (0.14, 10.88)	2.34 (0.26, 22.45)	3.62 (0.09, 282.60)	3.97 (0.54, 31.48)	0.30 (0.02, 5.30)	2.48 (0.10, 79.48)	0.75 (0.06, 8.84)	—				
IM TE, 250 mg/4 wk	1.50 (0.17, 17.85)	6.29 (0.17, 438.20)	1.97 (0.18, 28.25)	1.69 (0.17, 22.80)	1.71 (0.15, 24.04)	0.17 (0.01, 4.16)	0.93 (0.08, 13.60)	1.79 (0.16, 26.56)	2.89 (0.06, 247.30)	3.05 (0.29, 43.16)	0.23 (0.01, 5.19)	1.98 (0.07, 76.59)	0.57 (0.04, 10.68)	0.77 (0.04, 17.35)	—			
IM TE, 300 mg/3 wk	0.66 (0.11, 3.75)	2.68 (0.11, 121.80)	0.87 (0.12, 6.50)	0.75 (0.11, 4.89)	0.75 (0.10, 5.83)	0.07 (0.00, 1.03)	0.40 (0.05, 3.06)	0.79 (0.10, 6.08)	1.24 (0.03, 75.26)	1.37 (0.18, 9.49)	0.10 (0.01, 1.51)	0.84 (0.04, 25.16)	0.25 (0.02, 2.50)	0.34 (0.02, 4.14)	0.44 (0.02, 6.88)	—		
IM TE, 50-400 mg/wk	0.57 (0.01, 15.72)	2.38 (0.02, 250.90)	0.76 (0.02, 24.24)	0.63 (0.01, 19.41)	0.64 (0.01, 21.71)	0.06 (0.00, 3.14)	0.35 (0.01, 11.62)	0.70 (0.02, 21.69)	1.10 (0.01, 170.80)	1.16 (0.03, 36.05)	0.09 (0.00, 4.41)	0.72 (0.01, 59.92)	0.22 (0.00, 8.65)	0.28 (0.00, 13.36)	0.37 (0.00, 22.03)	0.84 (0.01, 35.23)	—	
IM TC, 200 mg/2 wk	4.60 (0.63, 41.23)	19.26 (0.62, 985.50)	6.06 (0.65, 66.60)	5.18 (0.59, 53.21)	5.23 (0.54, 58.01)	0.51 (0.02, 10.62)	2.83 (0.30, 31.83)	5.48 (0.58, 66.53)	8.83 (0.20, 628.00)	9.36 (1.01, 103.80)	0.70 (0.04, 13.20)	5.90 (0.23, 192.50)	1.77 (0.13, 27.17)	2.35 (0.14, 44.09)	3.16 (0.12, 63.54)	7.05 (0.48, 111.90)	8.04 (0.16, 617.30)	—

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

PARTICIPANT AGE

CARDIOVASCULAR DEATH

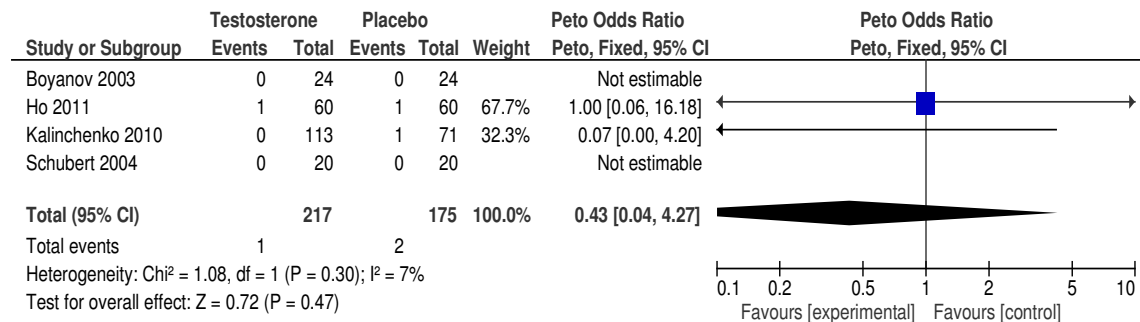
Of the 14 trials that reported cardiovascular death during the treatment period, 4 involved participants aged less than 65 years (31, 37, 39, 40) and 2 involved participants aged 65 years and older (3, 36) (Table 4.36). The remaining trials included a mixture of participants aged less than and more than 65 years.

TABLE 4.36: CHARACTERISTICS OF TRIALS THAT REPORTED CARDIOVASCULAR DEATH, BY AGE

Trial	Population	Duration	Treatment	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65 yr						
Ho 2011	At least mild testosterone deficiency syndrome	42 wk	Placebo	53.0 (8.2)	8.9 (2)	1/60
			IM TU, 1000 mg/12 wk	53.4 (7.4)	9.1 (1.8)	1/60
Kalinchenko 2010	MetS	30 wk	Placebo	52.8 (9.67)	7.5 (5.2)	1/71
			IM TU, 1000 mg/12wk	51.6 (9.76)	6.7 (3.0)	0/113
Schubert 2004	Primary or secondary hypogonadism	30 wk	IM TU 1000 mg/9 wk	41.1 (13.4)	3.9 (4.4)	0/20
			IM TE, 250 mg/3 wk	36.3 (12.3)	2.7 (2.3)	0/20
Boyano 2003	T2DM, obesity, and “symptoms of andropause or erectile dysfunction”	3 mo	No treatment	All: 57.5 (4.8)	10.76 (11.20)	0/24
			Oral TU, 120 mg/d	(NR by group)	9.56 (2.33)	0/24
> 65 yr						
Amory 2004	T below the range of normal for young adult men	36 mo	Placebo	71 (4)	10.1 (2.1)	0/24
			TE, IM, 200 mg/2wk	71 (4)	9.9 (1.6)	0/24
Basaria 2010	Limited mobility	6 mo	Placebo	74 (5)	8.2 (2.3)	0/103
			Gel 1%, 100 mg/d	74 (6)	8.7 (2.0)	1/106
Note: TE = testosterone enanthate, IM = intramuscular injection, MetS = metabolic syndrome, NR = not reported, SD = standard deviation, T2DM = type 2 diabetes mellitus, T = testosterone, TU = testosterone undecanoate.						

Among the 4 trials involving participants aged less than 65 years reported cardiovascular death during the treatment period (Table 4.36), 1 event was reported in a testosterone group (n = 217) and 2 events were reported in the placebo group (n = 175), giving an odds ratio of cardiovascular death associated with the use of testosterone of 0.43 (95% CI 0.04 to 4.27; $I^2 = 7\%$) (Figure 4.30).

FIGURE 4.30: ODDS OF CARDIOVASCULAR DEATH AMONG PARTICIPANTS AGED LESS THAN 65 YEARS



Among the 2 trials involving participants aged 65 years or older, 1 trial reported zero events in either group (36). Basaria and colleagues (3) reported that 1 cardiovascular death occurred in the testosterone treatment group ($n = 106$) and that zero events occurred in the placebo group ($n = 103$), giving an odds ratio of 7.18 (95% CI 0.14 to 362.14) (Table 4.36).

MYOCARDIAL INFARCTION

Of the 10 trials that reported myocardial infarction during the treatment period, 2 involved participants aged less than 65 years (31, 40) and 3 involved participants aged 65 years or older (3, 32, 44) (Table 4.37).

Among participants aged 65 years and younger, 2 events were reported in the testosterone group ($n = 173$), and 2 were reported in the placebo group ($n = 131$), giving an odds ratio of 0.89 (95% CI 0.12 to 6.48; $I^2 = 48\%$) (Figure 4.31).

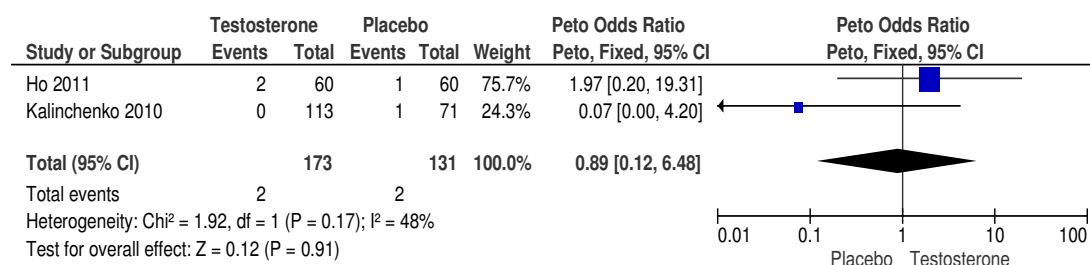
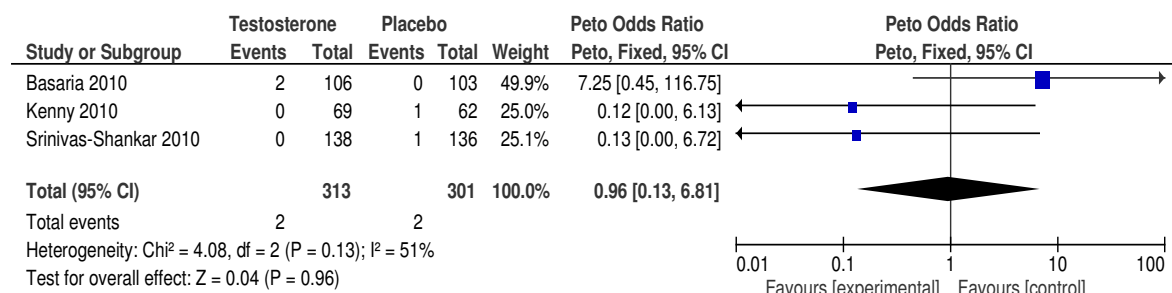
Among participants aged older than 65 years, 2 events were reported in the testosterone group ($n = 313$) and 2 events were reported in the placebo group ($n = 301$), giving an odds ratio of 0.96 (95% CI 0.13 to 6.81; $I^2 = 51\%$) (Figure 4.32).

Most of the trials included a wide range of participant ages, making the availability of data for analysis by participant age ($> v. \geq 65$ yr) limited. The results of the analyses presented below should be interpreted with caution because the findings are based on limited data.

TABLE 4.37: CHARACTERISTICS OF TRIALS THAT REPORTED MYOCARDIAL INFARCTION, BY AGE

Trial	Population	Duration	Treatment	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65 yr						
Ho 2011	At least mild testosterone deficiency syndrome	42 wk	Placebo	53.0 (8.2)	8.9 (2)	1/60
			IM TU, 1000 mg/12 wk	53.4 (7.4)	9.1 (1.8)	2/60
Kalinchenko 2010	MetS	30 wk	Placebo	52.8 (9.67)	7.5 (5.2)	1/71
			IM TU, 1000 mg/12wk	51.6 (9.76)	6.7 (3.0)	0/113
≥ 65 yr						
Kenny 2010	Low bone mass and physical frailty	24 mo	Placebo	76.3 (8.0)	14.5 (6.7)	1/62
			Gel 1%, 5 mg/d	77.9 (7.3)	13.2 (6.2)	0/69
Basaria 2010	Limited mobility	6 mo	Placebo	74 (5)	8.2 (2.3)	0/103
			Gel, 100 mg/d	74 (6)	8.7 (2.0)	2/106
Srinivas-Shankar 2010	Intermediate-frail and frail	6 mo	Placebo	73.9 (6.4)	10.9 (3.1)	1/136
			Gel 1%, 50 mg/d	73.7 (5.7)	11 (3.2)	0/138

Note: IM = intramuscular injection, MetS = metabolic syndrome, SD = standard deviation, T = testosterone, TU = testosterone undecanoate.

FIGURE 4.31: ODDS OF MYOCARDIAL INFARCTION AMONG PARTICIPANTS AGED LESS THAN 65 YEARS

FIGURE 4.32: ODDS OF MYOCARDIAL INFARCTION AMONG PARTICIPANTS AGED MORE THAN 65 YEARS


STROKE

Of the 4 trials that reported stroke during the treatment period, 2 involved participants aged 65 years or older (3, 36) (Table 4.38). No trials involved participants aged less than 65 years.

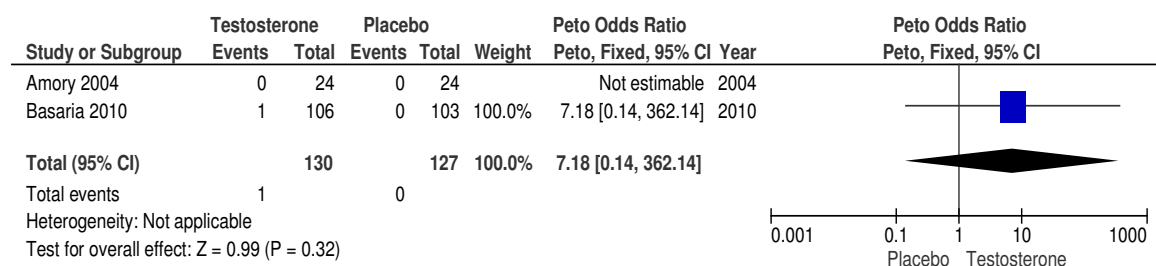
TABLE 4.38: CHARACTERISTICS OF TRIALS THAT REPORTED STROKE, BY AGE

Trial	Population	Duration	Treatment	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65 yr						
No trials						
≥ 65 yr						
Basaria 2010	Limited mobility	6 mo	Placebo	74 (5)	8.2 (2.3)	0/103
			Gel 1%, 100 mg/d	74 (6)	8.7 (2.0)	1/106
Amory 2004	T below the range of normal for young adult men	36 mo	Placebo	71 (4)	10.1 (2.1)	0/24
			IM TE, 200 mg/2wk	71 (4)	9.9 (1.6)	0/24

Note: TE = testosterone enanthate, IM = intramuscular injection, SD = standard deviation, T = testosterone.

Zero events were reported in either group in the trial by Amory and colleagues (36), while 1 stroke was reported in the testosterone group (n = 106) in the trial by Basaria and colleagues (3), with zero events in the placebo group (n = 103). The odds ratio of stroke associated with the use of testosterone based on this trial is 7.18 (95% CI 0.14 to 362.14) (Figure 4.33).

FIGURE 4.33: ODDS OF STROKE AMONG PARTICIPANTS AGED MORE THAN 65 YEARS



PROSTATE CANCER

Of the 11 trials that reported the development of prostate cancer during the treatment period, 1 involved participants aged less than 65 years (51), and 7 involved participants aged 65 years and older (3, 32, 36, 44, 47-49) (Table 4.39).

TABLE 4.39: CHARACTERISTICS OF TRIALS THAT REPORTED PROSTATE CANCER, BY AGE

Trial	Population	Duration	Treatment (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65 yr						
Dobs 1999	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33)	44.3 (11.1)	5.8 (2.7)	1/33
			IM TE, 200 mg/2wk (33)	44.9 (11.6)	6.3 (3.3)	2/33
≥ 65 yr						
Shigehara 2011	Benign prostate hypertrophy	12 mo	No treatment (26)	68.9 (9.1)	Free T, pg/ml	0/26
			IM TE, 250 mg/4 wk (26)	72 (6.5)	6.7 (1.9) 7.0 (1.7)	0/26
Kenny 2010	Low bone mass and physical frailty	12–24 mo	Placebo (62)	76.3 (8.0)	14.5 (6.7)	1/62
			Gel 1%, 5 mg/d (69)	77.9 (7.3)	13.2 (6.2)	1/69
Basaria 2010	Limited mobility	6 mo	Placebo (103)	74 (5)	8.2 (2.3)	0/103
			Gel 1%, 100 mg/d (106)	74 (6)	8.7 (2.0)	1/106
Srinivas- Shankar 2010	Intermediate- frail and frail	6 mo	Placebo (136)	73.9 (6.4)	10.9 (3.1)	1/136
			Gel 1%, 50 mg/d (138)	73.7 (5.7)	11 (3.2)	0/138
Emmelot- Vonk	Moderately low T levels	26 wk	Placebo (117)	67.4 (4.9)	10.4 (1.9)	2/117
			Oral TU, 160 mg/d (120)	67.1 (5.0)	11.0 (1.9)	0/138
Marks 2006	Symptoms of late-onset hypogonadism	6 mo	Placebo (22)	68 (NR)	8.7 (1.6)	4/22
			IM TE, 150 mg/2wk (22)	70 (NR)	7.7 (1.4)	2/22
Amory 2004	T below the range of normal for young men	36 mo	Placebo (24)	71 (4)	10.1 (2.1)	1/24
			IM TE, 200 mg/2wk (24)	71 (4)	9.9 (1.6)	2/24
Note: TE = testosterone enanthate, IM = intramuscular injection, SD = standard deviation, T = testosterone, TU = testosterone undecanoate.4						

In the trial by Dobs and colleagues (51), 2 events were reported in the testosterone group (n = 33) and 1 event was reported in the placebo group (n = 33), giving an odds of prostate cancer associated with the use of testosterone of 1.99 (95% CI 0.20 to 19.82) (Figure 4.34).

Among the trials that involved participants aged 65 years and older, 6 events were reported in the testosterone group (n = 505) and 9 events were reported in the placebo group (n = 490), giving an odds ratio of 0.64 (95% CI 0.23 to 1.82; $I^2 = 0\%$) (Figure 4.35).

FIGURE 4.34: ODDS OF PROSTATE CANCER AMONG PARTICIPANTS AGED LESS THAN 65 YEARS

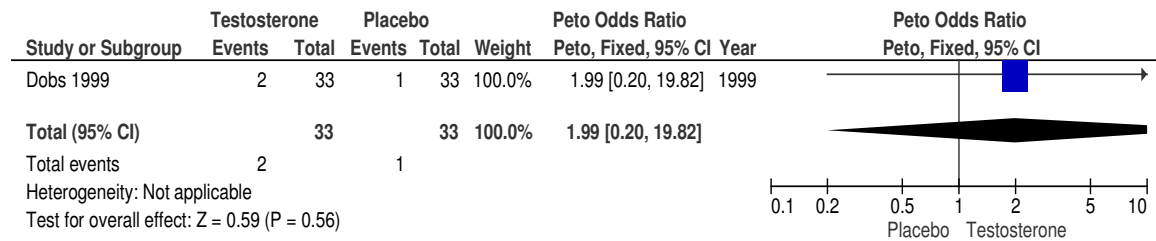
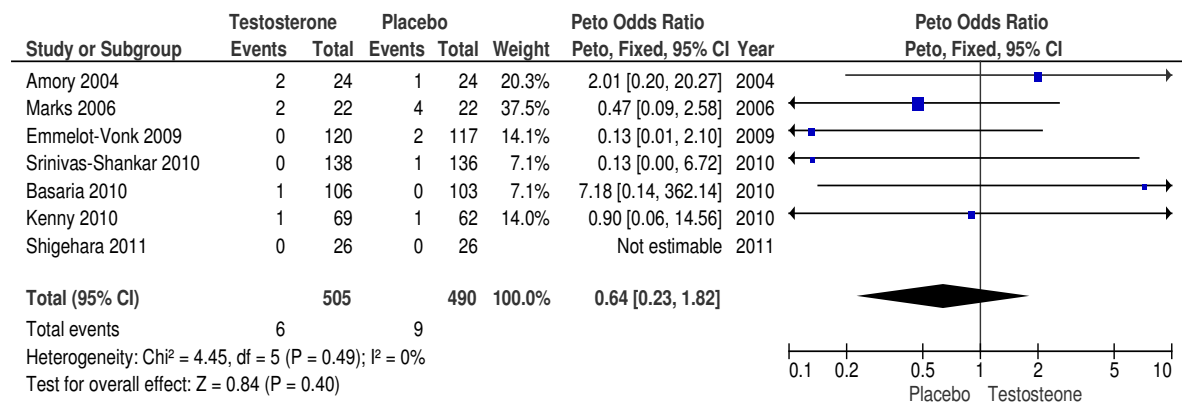


FIGURE 4.35: ODDS OF PROSTATE CANCER AMONG PARTICIPANTS AGED MORE THAN 65 YEARS



SERIOUS ADVERSE EVENTS

Of the 13 trials that reported serious adverse events during the treatment period, 5 involved participants aged less than 65 years (39, 40, 52, 53, 55), and 3 involved participants aged more than 65 years (3, 32, 48) (Table 4.40).

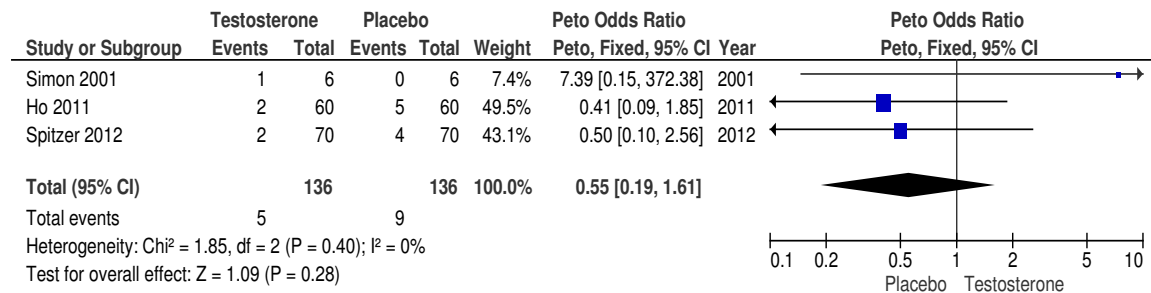
TABLE 4.40: CHARACTERISTICS OF TRIALS THAT REPORTED SERIOUS ADVERSE EVENTS, BY AGE

Trial	Population	Duration	Treatment	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65						
Spitzer 2012	Erectile dysfunction	14 wk	Placebo	54.6 (8.5)	8.8 (2.4)	4/70
			Gel 1%, 100 mg/d	55.1 (8.3)	8.6 (2.2)	2/70
Ho 2011	At least mild testosterone deficiency syndrome	42 wk	Placebo	53.0 (8.2)	8.9 (2)	5/60
			IM TU, 1000 mg/12 wk	53.4 (7.4)	9.1 (1.8)	2/60
Raynaud 2008	Hypogonadal men	6 mo	Patch, 4.8 mg/d	42.0 (12.7)	4.6 (3.2)	9/188
			IM TE, 250 mg/3 wk	40.7 (10.5)	5.1 (3.3)	3/36
Schubert 2004	Primary or secondary hypogonadism	30 wk	IM TU 1000 mg/9 wk	41.1 (13.4)	3.9 (4.4)	0/20
			IM TE, 250 mg/3 wk	36.3 (12.3)	2.7 (2.3)	0/20
Simon 2001	Healthy adult men	3 mo	Placebo	55.4 (3.6)	9.4 (1.0)	0/6
			Gel, 125 mg/d	52.8 (4.2)	8.3 (0.3)	1/6
> 65 yr						
Basaria 2010	Limited mobility	6 mo	Placebo	74 (5)	8.2 (2.3)	8/103
			Gel 1%, 100 mg/d	74 (6)	8.7 (2.0)	16/106
Srinivas- Shankar 2010	Intermediate- frail and frail	6 mo	Placebo	73.9 (6.4)	10.9 (3.1)	3/136
			Gel 1%, 50 mg/d	73.7 (5.7)	11 (3.2)	6/138
Emmelot- Vonk, 2009	Moderately low T levels	26 wk	Placebo	67.4 (4.9)	10.4 (1.9)	10/117
			Oral TU 160 mg/d	67.1 (5.0)	11.0 (1.9)	5/120
Note: TE = testosterone enanthate, IM = intramuscular injection, SD = standard deviation, T = testosterone, TU = testosterone undecanoate.						

LESS THAN 65 YEARS

Among the trials that involved participants aged less than 65 years, 3 involved comparison between a testosterone product and placebo (40, 52, 55). Five events were reported in the testosterone group (n = 136), and 9 events were reported in the placebo group (n = 136), giving an odds of a serious adverse event associated with testosterone of 0.55 (95% CI 0.19 to 1.61; $I^2 = 0$) (Figure 4.36).

FIGURE 4.36: ODDS OF A SERIOUS ADVERSE EVENT AMONG PARTICIPANTS AGED LESS THAN 65 YEARS



Two trials involving participants aged less than 65 years were head-to-head trials of testosterone replacement therapies. In the trial by Schubert and colleagues (39), zero serious adverse events were reported in the intramuscular testosterone undecanoate group (1000 mg/12 wk; $n = 20$) and in the intramuscular testosterone enanthate group (250 mg/3 wk; $n = 20$). In the trial by Raynaud and colleagues (53), 9 serious adverse events were reported in the testosterone patch group ($n = 188$), and 3 events were reported in the intramuscular testosterone enanthate group (250 mg/3wk; $n = 36$). The odds of a serious adverse event associated with the use of intramuscular testosterone enanthate compared with testosterone patch based on this trial were 2.01 (95% CI 0.41 to 9.74).

65 YEARS OR OLDER

All 3 trials that involved participants aged 65 years and older randomized participants to testosterone or placebo. In total, 27 events were reported in the testosterone group ($n = 364$), and 21 events were reported in the placebo group, giving an odds ratio of 1.28 (95% CI 0.71 to 2.30; $I^2 = 60\%$) (Figure 4.37).

The evidence network for serious adverse events by route of administration involved 3 treatments and a total of 720 participants. Three comparisons were made, based on 3 trials each with 2 arms (Figure 4.38).

FIGURE 4.37: ODDS OF A SERIOUS ADVERSE EVENT AMONG PARTICIPANTS AGED MORE THAN 65 YEARS

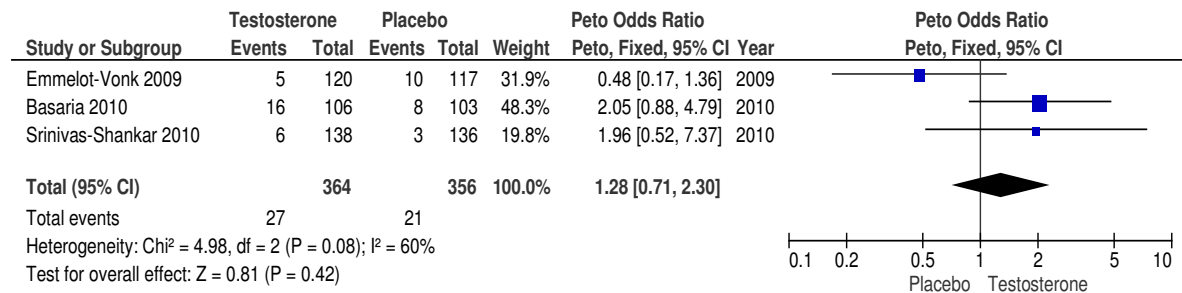
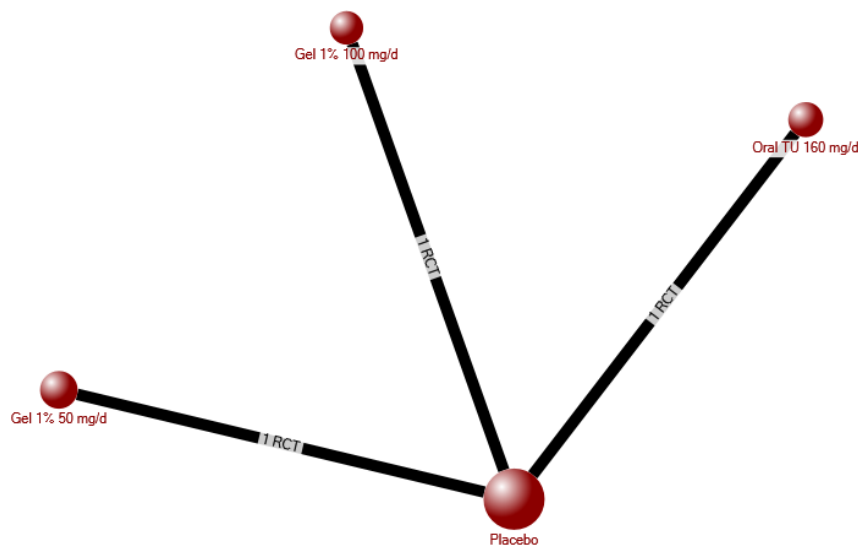


FIGURE 4.38: EVIDENCE NETWORK FOR SERIOUS ADVERSE EVENTS AMONG PARTICIPANTS AGED 65 YEARS AND OLDER



There were no significant differences in the odds of a serious adverse event among participants aged 65 years and older between placebo and any of the testosterone treatments included in the network, and there were no significant differences among the treatments (Table 4.42).

TABLE 4.41: SERIOUS ADVERSE EVENTS, AGE 65 YEARS AND OLDER — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1% 50 mg/d	Gel 1% 100 mg/d	Oral TU 160 mg/d
Gel 1% 50 mg/d	1.81 (0.34, 10.26)	—		
Gel 1% 100 mg/d	2.03 (0.52, 7.92)	1.12 (0.12, 9.80)	—	
Oral TU 160 mg/d	0.45 (0.09, 2.02)	0.25 (0.02, 2.36)	0.22 (0.03, 1.70)	—

Note: TU = testosterone undecanoate

WITHDRAWALS DUE TO ADVERSE EVENTS

Of the 40 trials that reported withdrawals due to adverse events, 10 involved participants aged less than 65 years (31, 37, 39, 40, 51, 52, 57, 59, 63, 64) and 7 involved participants aged 65 years and older (3, 32, 36, 44, 48, 49, 70) (Table 4.42).

TABLE 4.42: CHARACTERISTICS OF TRIALS THAT REPORTED WITHDRAWALS DUE TO ADVERSE EVENTS, BY AGE

Trial	Population	Duration	Treatment (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
< 65 yr						
Spitzer 2012	Erectile dysfunction	14 wk	Placebo (70)	54.6 (8.5)	8.8 (2.4)	1/70
			Gel 1%, 100 mg/d (70)	55.1 (8.3)	8.6 (2.2)	5/70
Ho 2011	At least mild AMS symptoms	42 wk	Placebo (60)	53.0 (8.2)	8.9 (2)	2/60
			IM TU, 1000 mg/12 wk (60)	53.4 (7.4)	9.1 (1.8)	2/60
Kalinchenko 2010	MetS	30 wk	Placebo (71)	52.8 (9.67)	7.5 (5.2)	3/71
			IM TU, 1000 mg/12wk (113)	51.6 (9.76)	6.7 (3.0)	1/113
Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16)	55.9 (6)	10.4 (0.8)	0/16
			Gel 1%, 50 mg/d (16)	57.3 (5.6)	10.5 (0.8)	0/16
Schubert 2004	Primary or secondary hypogonadism	30 wk	IM TU, 1000 mg/9 wk (20)	41.1 (13.4)	3.9 (4.4)	0/20
			IM TE, 250 mg/3 wk (20)	36.3 (12.3)	2.7 (2.3)	0/20
Cavallini 2004	Symptoms of androgen decline	6 mo	Placebo (45)	63 (NR)	10.5 (2.1)	0/45
			Oral TU, 160 mg/d (40)	64 (NR)	9.9 (1.8)	0/40
Boyanov 2003	T2DM, obesity, and “symptoms of andropause or erectile dysfunction”	3 mo	No treatment (24)	All: 57.5	10.76 (11.20)	0/24
			Oral TU, 120 mg/d (24)	(4.8) (NR by group)	9.56 (2.33)	0/24

Trial	Population	Duration	Treatment (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	No. of events
Bhasin 2000	HIV-infected with weight loss	16 wk	Placebo (14) IM TE, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	0/14 0/17
Dobs 1999	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	0/33 1/33
Grinspoon 1998	AIDS wasting syndrome	6 mo	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	4/26 3/26
> 65 yr						
Basaria 2010	Limited mobility	6 mo	Placebo (103) Gel 1%, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	14/103 13/106
Kenny 2010	Low bone mass and physical frailty	12–24 mo	Placebo (62) Gel 1%, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	26/62 24/68
Srinivas- Shankar 2010	Intermediate- frail and frail	6 mo	Placebo (136) Gel 1%, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	9/136 10/138
Emmelot- Vonk, 2009	Moderately low T levels	26 wk	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	12/117 11/120
Marks 2006	Symptoms of late-onset hypogonadism	6 mo	Placebo (22) IM TE, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	1/22 1/22
Amory 2004	T below the range of normal for young adult men	36 mo	Placebo (24) IM TE, 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	2/24 5/24
Tan 2003	Alzheimer's disease	12 mo	Placebo (5) IM TE, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	0/5 1/5
Note: MetS = metabolic syndrome, NR = not reported, T2DM = type 2 diabetes mellitus, T= testosterone, TE = testosterone enanthate, TRT = testosterone replacement therapy.						

LESS THAN 65 YR

The evidence network for withdrawals due to adverse events among participants 65 years and less included 9 trials involving 732 participants. Eight treatments were included in the network, giving 9 comparisons based on 9 trials each with 2 arms (Table 4.39).

There were no significant differences in the odds of a withdrawal due to adverse events among participants aged less than 65 years between placebo and any of the testosterone treatments, and there were no significant differences among the treatments (Table 4.43).

FIGURE 4.39: EVIDENCE NETWORK FOR WITHDRAWALS AMONG PARTICIPANTS AGED LESS THAN 65 YEARS

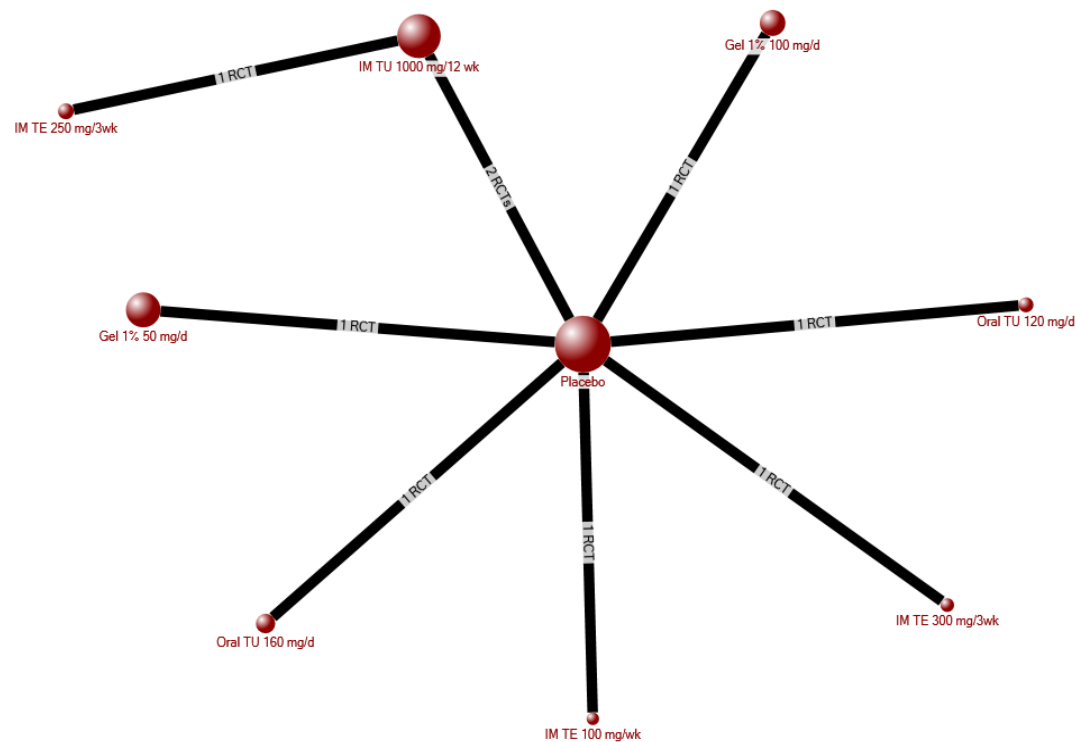


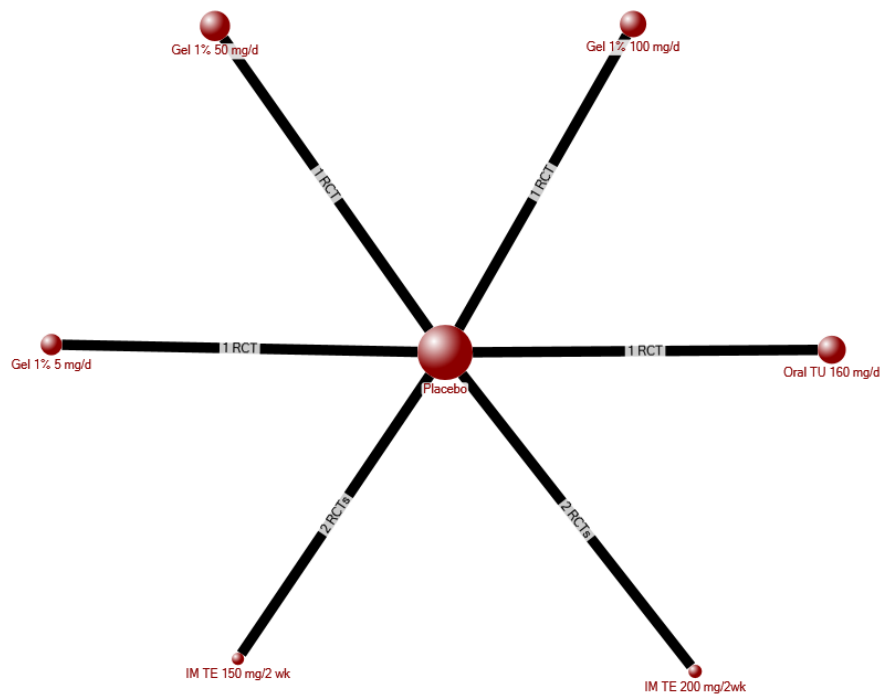
TABLE 4.43: WITHDRAWALS DUE TO ADVERSE EVENTS, AGE LESS THAN 65 YEARS — ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 100 mg/ wk	IM TE, 250 mg/3 wk	IM TE, 300 mg/3 wk
Gel 1%, 50 mg/d	0.56 (0.01, 14.89)	—							
Gel 1%, 100 mg/d	3.63 (0.53, 33.50)	6.76 (0.15, 574.10)	—						
Oral TU 120 mg/d	0.56 (0.01, 14.74)	0.97 (0.01, 193.10)	0.15 (0.00, 6.99)	—					
Oral TU 160 mg/d	0.46 (0.01, 10.84)	0.84 (0.01, 127.70)	0.12 (0.00, 5.35)	0.83 (0.01, 109.30)	—				
IM TU, 1000 mg/12 wk	0.44 (0.09, 1.99)	0.79 (0.02, 52.38)	0.12 (0.01, 1.36)	0.79 (0.02, 51.48)	0.95 (0.03, 55.93)	—			
IM TE, 100 mg/ wk	0.63 (0.01, 17.01)	1.12 (0.01, 176.40)	0.17 (0.00, 7.48)	1.13 (0.01, 151.90)	1.34 (0.01, 250.60)	1.41 (0.02, 52.74)	—		
IM TE, 250 mg/3 wk	0.32 (0.01, 10.36)	0.58 (0.00, 87.76)	0.08 (0.00, 4.95)	0.57 (0.00, 107.50)	0.71 (0.01, 128.20)	0.74 (0.02, 21.23)	0.53 (0.00, 96.42)	—	
IM TE, 300 mg/3 wk	0.68 (0.10, 4.18)	1.21 (0.03, 89.33)	0.18 (0.01, 2.63)	1.21 (0.03, 83.48)	1.52 (0.04, 100.70)	1.54 (0.14, 16.55)	1.11 (0.02, 92.76)	2.14 (0.04, 120.00)	—
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.									

65 YEARS OR OLDER

The evidence network for withdrawals due to adverse events among participants 65 years and less included 7 trials involving 952 participants. Six treatments were included in the network, giving 7 comparisons based on 7 trials each with 2 arms (Figure 4.40).

FIGURE 4.40: EVIDENCE NETWORK FOR WITHDRAWALS AMONG PARTICIPANTS AGED 65 YEARS AND OLDER



There were no significant differences in the odds of withdrawal due to adverse events among participants aged 65 years or older between placebo and any testosterone treatment, and there were no significant differences among the treatments (Table 4.44).

TABLE 4.44: WITHDRAWALS DUE TO ADVERSE EVENTS, AGE 65 YEARS AND OLDER— ODDS RATIO (95% CREDIBLE INTERVAL)

	Placebo	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TE, 100 mg/ wk	IM TE, 200 mg/3 wk
Gel 1%, 5 mg/d	0.76 (0.24, 2.42)	—					
Gel 1%, 50 mg/d	1.08 (0.29, 3.95)	1.42 (0.25, 8.01)	—				
Gel 1%, 100 mg/d	0.88 (0.26, 2.91)	1.16 (0.22, 6.00)	0.81 (0.14, 4.74)	—			
Oral TU 160 mg/d	0.86 (0.25, 2.98)	1.14 (0.21, 6.11)	0.79 (0.13, 4.85)	0.98 (0.18, 5.48)	—		
IM TE, 150 mg/2wk	0.76 (0.03, 11.81)	1.00 (0.04, 19.73)	0.70 (0.03, 15.08)	0.86 (0.03, 17.51)	0.88 (0.03, 18.00)	—	
IM TE, 200 mg/2wk	2.64 (0.57, 13.86)	3.53 (0.50, 26.21)	2.46 (0.33, 20.45)	3.02 (0.43, 22.74)	3.08 (0.42, 23.63)	3.52 (0.15, 113.90)	—
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.							

COMORBIDITIES

DIABETES MELLITUS

Two trials included men with type II diabetes. Hackett and colleagues (46) reported the occurrence of prostate cancer, serious adverse events, and withdrawals due to adverse events during their trial. Each of these events was more frequent in the placebo group than in the control group (Table 4.45). No adverse events were reported by Boyanov and colleagues (37).

Four studies included men with type II diabetes and metabolic syndrome (30, 42, 43, 64). No adverse events were reported in the trial by Heufelder and colleagues (64), which involved a supervised diet and exercise program administered to each group, in addition to either placebo or testosterone treatment. In the trial by Jones and colleagues (30), the authors report that 17 serious adverse events were experienced by 13 patients; however, the group to which these patients belonged was not reported. They do, however, report that 1 patient in the placebo group died as a result of myocardial infarction, and that 18 patients withdrew from the testosterone group and 12 from the placebo group. The authors state that the most common reasons for withdrawals were “skin and subcutaneous tissue disorders.” In the trial

by Aversa and colleagues (42), the authors report that 1 patient withdrew from placebo arm because of myocardial infarction and that 1 patient withdrew from the intramuscular testosterone undecanoate arm because of mild "heritrocytosis"; however, because of the trial design and reporting, we were unable to include these events in our analysis (all patients in the oral testosterone undecanoate group were switched to the intramuscular testosterone group; data not reported by period). The authors also stated that 2 patients discontinued treatment because of "prostate events" but the group from which they withdrew was not reported. In an additional trial by Aversa and colleagues (43), 1 patient in the placebo group withdrew because of myocardial infarction and that 3 patients in the testosterone group withdrew because of mild erythrocytosis.

One trial involved participants with metabolic syndrome (31). Kalichenko and colleagues (31) reported 1 withdrawal due to adverse events in the testosterone group (shrinkage of testis volume) and 3 in the placebo group (abscess following injection, death [unknown cause], death [myocardial infarction]).

DEPRESSION

Two trials enrolled participants with diagnosed depression (69, 74) (Table 4.46). Two patients withdrew early from the trial by Orengo and colleagues (74) because of worsening medical conditions; however, to which group these participants were randomized was not reported. Five patients withdrew early from the trial by Shores and colleagues (69) because of adverse events: 1 from the placebo arm because of worsening sleep apnea, and 3 from the testosterone group because of skin irritation, psychiatric instability, and alcohol abuse. No cardiovascular death, myocardial infarction, stroke, prostate cancer or serious adverse events were reported in these 2 trials.

TABLE 4.45: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS OR METABOLIC SYNDROME

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Outcomes of interest
T2DM						
Hackett 2013	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	• PCA: P 1/102; T 0/97 • SAE: P 3/102; T 1/97 • WAE: P 4/102; T 0/97
Boyanov 2003	T2DM, obesity, and "symptoms of andropause or [ED]"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	"No adverse events were reported during the study"
MetS or T2DM						
Jones 2011	MetS or T2DM with ≥ 2 symptoms of hypogonadism	12 mo	Placebo (112) 2% gel, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	9.5 (3.3) 9.2 (2.6)	• CV death: P 1/112; T 0/108 • MI: P 1/112; T 0/108 • WAE: P 12/112; T 18/180
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32) *After the first 6 months, patients in the oral TU group were switched to the IM TU group; data not reported by period	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	"At last observation carried forward, there were two discontinuations due to prostate adverse events. One patients withdrew in the IM TU arm (mild and transient heritocytosis) and one in the P arm (acute myocardial infarction)." "There were no serious adverse drug reactions recorded during the study."
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	"One patient in the PLB group experienced an acute myocardial infarction and three patients in the TU group experienced mild erythrocytosis."
Heufelder 2009	MetS and newly diagnosed diabetes	52 wk	Placebo (16) Gel 1%, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	"All participants completed the study without adverse effects and without protocol violations..."
METS						
Kalinchenko 2010	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	• CV death: P 1/71; 0/113 • MI: 1/71; 0/113 • WAE: P 3/71; T 1/113
Note: ED = erectile dysfunction, IM = intramuscular injection, MetS = metabolic syndrome, NR = not reported, QoL = quality of life, SD = standard deviation, T = testosterone, T2DM = type 2 diabetes mellitus, TU = testosterone undecanoate.						

TABLE 4.46: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH DEPRESSION

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcome of interest
Shores 2009	Dysthymia or minor depression	12 wk	Placebo (16) Gel 1%, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	"One subject was dropped from the placebo arm due to complaints of worsening sleep apnea. In the testosterone arm, 4 stopped the protocol for the following reasons: dislike of the smell of the gel, skin irritation from the gel, psychiatric instability after a death in the family and concurrent alcohol abuse (that had been denied at the initial interview."
Orengo 2005	Treatment- resistant depression	12 wk	Placebo (5) Gel 1%, 50 mg/d (7)	All: 63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	"Of the 6 participants who dropped out of the study, ... 2 had worsening of previous medical conditions" (type and treatment group not reported)

Note: QoL = quality of life, SD = standard deviation, T = testosterone.

OBESITY

One study involved patients with obesity (waist-hip ratio ≥ 0.9) (37): no adverse events were reported in the study (Table 4.47).

TABLE 4.47: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH OBESITY

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcome of interest
Boyanov 2003	T2DM, visceral obesity,* and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	"No adverse events were reported during the study." "All subjects completed the study in accordance with the protocol."

Note: NR = not reported, SD = standard deviation, T2DM = type 2 diabetes mellitus, T = testosterone.
*Obesity was defined by Boyanov and colleagues as waist-hip ratio ≥ 0.9

CORONARY ARTERY DISEASE

One trial included men with coronary artery disease (75) (Table 4.48). The published record of this trial contains no mention of adverse events or number of participants who completed the trial (75). Two trials involved participants with chronic heart failure (33, 76): Stout and

colleague (76) did not report withdrawals in a useable way, while the Caminiti and colleagues (33) reported that the reasons for the 4 withdrawals from the testosterone group and 2 from the placebo group were not related to treatment. The trial by Mathur and colleagues (77) involved participants with chronic angina: 1 patient from each group withdrew before the end of the trial, but the reasons for withdrawal were not reported.

TABLE 4.48: CHARACTERISTICS OF TRIALS THAT INVOLVED PARTICIPANTS WITH CORONARY ARTERY DISEASE

Trial	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline total T, mean (SD), nmol/L	Outcomes of interest
Coronary artery disease						
Kang 2002	Coronary artery disease	12 wk	Placebo (17) Oral TU, 160 mg/d (18)	58 (9) 57 (7)	Free T, pg/ml 13.8 (1.8) 9.9 (3.1)	No reporting of harms data
Other coronary comorbidities						
Stout 2012	Chronic heart failure	12 wk	Placebo (20) Sustanon,* 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	12 dropouts reported (6 WAE), but not by group assignment
Caminiti 2009	Chronic heart failure	12 wk	Placebo (35) IM TU, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	“Of 70 patients, 64 completed the study protocol: 4 patients in the testosterone group and 2 in the placebo group discontinued the study. The reason for discontinuation, in every case, was the willingness of the patient to escape from the study (e.g., logistic reasons, moving to another region, autonomous decision to discontinue the protocol not related to testosterone supplementation)”
Mathur 2009	Chronic angina pectoris	12 mo	Placebo (7) IM TU, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	1 dropout from each group reported but reasons not reported.
Note: IM = intramuscular injection, NA = not applicable, QoL = quality of life, SD = standard deviation, T = testosterone.						

HYPERLIPIDEMIA

No trials were included that specifically enrolled participants with hyperlipidemia.

HYPERTENSION

No trials were included that specifically enrolled participants with hypertension.

4.3.5 EVIDENCE FROM NON-RANDOMIZED INTERVENTIONAL STUDIES

A total of 38 unique non-randomized studies of interventions ("non-randomized studies") (40 reports) met our inclusion criteria. Of these, 26 studies did not report an outcome of interest (78-103). Twelve studies included at least 1 outcome of interest and are summarized in Table 4.49. The most frequently reported safety outcome was prostate cancer; however, the reporting was generally poor, primarily because of a lack of transparency around the number of patients in each group and the number of events per treatment.

TABLE 4.49: OUTCOMES REPORTED IN NON-RANDOMIZED STUDIES

Study	Population	Treatment (no. in group)	Outcome	Comments
Retrospective cohort				
Vigen 2013	Men who underwent coronary angiography at a VA medical centre	- No treatment (7486) - TRT, dose NR (1223) Mean follow-up: 840 d	- Cardiovascular events[†]: Absolute difference in TRT group 3 years after coronary angiography: 5.8% (−1.4% to 13.1%) - MI: no TRT: 23/1223; TRT: 420/7486 - Stroke: no TRT: 33/1223; TRT: 486/7486	Entry into cohort was based on filling a prescription for TRT (patch, gel, injectable; brands NR). Data reported as TRT v. no TRT (not by type of TRT). Raw data provided for MI, stroke and all-cause death, but length of follow-up differed by group. "Of the 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Of the 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes."
Shores 2012	> 40 yr treated at a VA medical center, inpatient or outpatient	- No treatment (633) - TRT (398) Duration: 20.2 mo	Prostate cancer: No treatment: 13/633 men; TRT: 7/398 men	Data reported as TRT v. no TRT (not by type of TRT). TRTs included injectable, patch, or gel (brands NR) "Diagnoses of incident prostate cancer during follow-up were similar between the two groups with 1.6% incident prostate cancer in the treated men compared with 2.0% incident prostate cancer in the untreated men (p= 0.68)."
Rhoden 2006	Hypogonadal men with negative prostate biopsy prior to starting TRT	- IM testosterone, dose and type NR (33) - Gel 1%, dose NR (25) Duration: 12 mo	Prostate cancer: 1 case in the IM group	"Six men (10.3%) had a PSA increase 41.0 ng/ml after 12 months of TRT. Four of these men underwent repeat prostate biopsy, and one of these had prostate cancer. He was 55-year-old with a baseline PSA of 5.5 ng/ml that rose to 8.2 ng/ml after 12 months of TRT, an increase of 2.7 ng/ml. An additional five men underwent repeat biopsy due to changes noted on DRE; however, no new cases of prostate cancer were identified in these men"
Guay 2000	Men with ED and primary or secondary hypogonadism	- IM TE, 200-300 mg/2-3 wk (25) - Patch, 5 mg/d (16) - Clomiphene citrate, oral, 50 mg/3x per wk (49) Duration: 2-3 mo	Prostate cancer: 3 cases (NR which treatment group the patients belonged to)	"Of the overall group of 90 patients, 10 were referred for ultrasonography and prostate biopsy. In two patients, biopsy specimens were positive for adenocarcinoma. In a third patient, biopsy studies were repeated because of an equivocal result, and the presence of prostate carcinoma was ultimately confirmed "

Study	Population	Treatment (no. in group)	Outcome	Comments
Prospective cohort				
Francomano 2014	Severely obese men (mean BMI 42) with ≥ 2 symptoms of hypogonadism	• DPE (12) • DPE + IM TU, 1000 mg/12 wk (12) Duration: 54 wk + 24 wk observational period following withdrawal of treatment	• WAE: zero in both groups • SAE: zero in both groups	4 dropouts were reported in the DPE group because of poor compliance with the study protocol. "No serious emergent adverse events were recorded for both treatments during the study."
Aydogdu 2013	IHH	• Sustanon, 250 mg/3wk (28) • Gel 1%, 50 mg/d (24) • hCG, 5000 IU, 2x/ wk (25) Duration: 24 wk	• SAE: zero in all groups • Skin reactions: 4/28 in Sustanon group	"No serious adverse events were detected with any of the treatment types" "Four patients showed sporadic signs of acne after TE injections."
Blick 2013	HIV/AIDS	• Androgel 1%, gel, 50 mg/d (92) • Testim 1%, gel, 50 mg/d (75) Duration: 12 mo	• Erythrocytosis: zero in both groups • Prostate cancer: zero in both groups • WAE: zero in both groups • Skin reactions were assessed but not reported	"No patients developed significant polycythemia ... or prostate cancer ..." "No patients discontinued therapy due to adverse events"
Aversa 2012	Middle-aged men with LOH and MetS	• No treatment (20) • IM TU, 12 wk (40) Duration: 36 mo	• MI: 1 in control group • Erythrocytosis: 4 in TU group	9 patients in the TU group are unaccounted for and presumed to have dropped out of the study (no reasons provided) "Of the 40-hypogonadal men enrolled in the prior long-term TU study and randomized to receive TRT, only 20 completed the entire 3 years duration phase and were included for statistical evaluation. In fact, in the TU group, four patients were discontinued because experienced mild and transient erythrocytosis, one patient for increased PSA levels, six patients for personal reasons and nine patients did not terminate the 36 months of observation. One patient in the control group experienced an acute myocardial infarction." "The study adherence was 50% and no serious adverse event related to T administration was reported."
Dean 2005	Aged 21–81 yrs	• Gel 1%, 50 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 371 men Duration: up to 12 mo	• Prostate cancer: 3 • WAE: 40 • SAE: 6 • Skin reactions: 5.9% of men	SAEs that affected more than 1% of participants reported, not all SAEs; authors reported only adverse events "judged related to study medication" "Three patients received a diagnosis of prostate cancer." "The most frequent adverse events leading to discontinuation were increased PSA level (2.4%), increased hematology parameters (2.4%), and application site reactions (1.1%)"

Study	Population	Treatment (no. in group)	Outcome	Comments
Wang 2004	Aged 19–68 yr	• Gel 1%, 50 mg/d (NR) • Gel 1%, 75 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 163 men Duration: 36 mo†	• Prostate cancer: 1 in 75 mg/d group, 2 in 100 mg/d group • Skin reactions: 12 men	No. of people in each group not reported “Of the subjects who had elevated PSA during the study, three had confirmed prostate cancer on biopsy. All three subjects were over 63 yr old at enrollment in the study.” “In addition to the prostate disease described above, there were two serious adverse events possibly related to treatment.” “Application site skin reaction occurred in 12 of 163 subjects (five, three, and four subjects were receiving 5, 7.5, and 10 g T gel/d), 11 had minimal or mild erythema, and one was classified as moderate. Only one subject discontinued from the study after 12 months of 5g T treatment because of worsening of minimal erythema and punctate rash” “Acne was noted in 12 subjects (7.4%).”
Morgunov 2011	T2DM, acquired androgen deficiency, and first episode of ischemic stroke	• No treatment (30) • IM TU 1000 mg/12 wk (42) Duration: 2 yr Mean age 61.4 yr	Stroke: 3 patients in the TRT group, 5 patients in the control group	Stroke reported as an outcome was second stroke
Hajjar 1997	Elderly men	• No treatment (27) • IM TE or TC 200mg/2-3 wk (45) Duration: at least 2 yr	Myocardial infarction: 1 in TRT group • TRT: 1/26 Stroke • No treatment: 1/23 • TRT: 1/26 Diabetes • No treatment: 0/23 • TRT: 1/26 Erythrocytosis* • No treatment: 0/27 • TRT: 11/45	Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted (Safety data provided for 23 participants in the control group and 26 in the TRT group, at 24 months. Prostate cancer was reported as “benign prostatic hypertrophy/prostate cancer”; the number of patients with prostate cancer was not reported (6/23 in control group; 2/26 in TRT group)
Note: BMI = body mass index, DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular injection, LOH = late-onset hypogonadism, MetS = metabolic syndrome, MI = myocardial infarction, NR = not reported, PSA = prostate specific antigen, SAE = serious adverse event, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, T2DM = type II diabetes mellitus, VA = Veterans Affairs, WAE = withdrawal due to adverse events. *Reported as polycythemia for the treatment group. Zero count inferred for the control group. †Composite outcome of all-cause mortality, myocardial infarction, and ischemic stroke. ‡ This study was completed after an initial 6-month randomized study for an additional 36 months; participants had a total of 42 months of gel exposure.				

CARDIOVASCULAR DEATH

Cardiovascular death was reported in 1 non-randomized study (25). Hajjar and colleagues (25) reported that 1 participant in the testosterone group died following a myocardial infarction. Their study enrolled 72 elderly men with low testosterone (mean age 72 yr in the

testosterone group). Of note, one-third of participants were not included in the safety analysis, and the reasons for (presumed) withdrawal from the study were not reported.

An additional study reported a composite outcome that included all-cause death, myocardial infarction, and stroke. Vigen and colleagues (4) performed a retrospective cohort study involving men with low testosterone who had undergone coronary angiography between 2005 and 2011 at a Veterans Affairs facility in the United States ($n = 8709$), with a mean follow-up time of 27.5 months. A total of 1710 events occurred during follow-up among those taking a testosterone product, compared to 681 events among 7486 patients not taking testosterone (absolute risk difference 5.8%, 95% CI -1.4% to 13.1%) 3 years after coronary angiography. After adjustment for the presence of coronary artery disease at baseline, the risk of an event was greater among men taking testosterone (hazard ratio 1.29, 95% CI 1.04–1.58) (4). In this study, most participants were receiving testosterone in the form of a patch (63.3%), followed by intramuscular testosterone (35.7%), and testosterone gel (1.1%). Of note, the before-treatment testosterone levels were not available, and it is unknown whether testosterone replacement therapy was appropriately prescribed to men with diagnosed hypogonadism.

MYOCARDIAL INFARCTION

Three non-randomized studies reported myocardial infarction (4, 25, 104). As described above, Vigen and colleagues (4) included myocardial infarction as part of a composite outcome in their retrospective cohort study. The authors report that 420 patients (5.6%; $n = 7486$), in the control group and 23 patients in the testosterone group (1.9%; $n = 1223$) experienced a myocardial infarction. Because the primary end point was time to event for a composite of death, MI, or stroke and cohort entry was censored at the time of the first event, the length of time at risk of each event may have been different between the control and treatment groups.

Hajjar and colleagues (25) performed a prospective cohort study involving 45 elderly men taking testosterone and 27 not taking testosterone. The products used were testosterone enanthate or cypionate (200 mg/2–3 wk). The authors report many adverse events including myocardial infarction, stroke, newly diagnosed diabetes, and erythrocytosis (Table 4.49); however, the data were poorly reported, and the number of people that their analyses are

based on is not clear (safety data only reported for about two-thirds of participants). One participant in the testosterone group died of a myocardial infarction.

In the non-randomized study by Aversa and colleagues (104) involving men with metabolic syndrome, 1 participant in the control group (n = 20) experienced a myocardial infarction. No events were reported in the intramuscular testosterone undecanoate group; however, not all participants are accounted for in the reporting of participant flow through the study.

STROKE

Stroke was reported in 3 non-randomized studies (4, 22, 25) (Table 4.49). In their retrospective cohort study, Vigen and colleagues (4) reported that 33 men in the testosterone group (2.7%; n = 1223) and 486 men in the control group experienced a stroke (6.5%; n = 7486).

Hajjar and colleagues (25) reported that 1 patient in each group experienced a stroke.

Morgunov and colleagues (22) reported stroke among men with type 2 diabetes mellitus who had previously experienced a stroke. In total, 3 patients in the testosterone group (n = 42), and 5 patients in the control group (n = 30) were reported to have experienced a second stroke during the study period.

PROSTATE CANCER

Prostate cancer was reported in 7 non-randomized studies (23-25, 105-108); however, the data were inconsistently reported. Of these, 4 were prospective cohorts and 3 were retrospective cohorts.

PROSPECTIVE COHORT

In the study by Wang and colleagues (108), all participants were taking 1% testosterone gel, at 50, 75 or 100 mg/d. The authors reported that 1 patient in the 75 mg/d group and 2 in the 100 mg/d group experienced prostate cancer. However, it was not reported how many participants were assigned to each treatment group.

Blick and colleagues (23) reported that no patients in either treatment group (AndroGel 1% v. Testim 1%, both 50 mg/d) developed prostate cancer during the study period.

Hajjar and colleagues (25) reported 2 case of “benign prostatic hypertrophy/prostate cancer” in the testosterone group and 6 cases in the control group. However, the authors did not separately report the data for prostate cancer, and we were unable to determine which of the reported cases were prostate cancer and which were benign.

Three cases of prostate cancer were reported in the study by Dean and colleagues (105), which compared 1% testosterone gel at 2 doses (50 mg/d v. 100 mg/d); however, the group in which the 3 cases occurred was not reported. Of note, the authors reported only serious adverse events “judged to be related to study medication,” and they reported only serious adverse events that affected more than 1% of participants.

RETROSPECTIVE COHORT

Shores and colleagues (107) performed a retrospective cohort study involving men aged more than 40 years receiving care at a Veterans Affairs Centre. The authors reported 7 cases of prostate cancer among men taking testosterone replacement therapy (n = 398) and 13 cases among men receiving no treatment (n = 633); this difference was not statistically significant between groups (p = 0.68). The mean duration of follow-up was 20 months, and the type and dose of testosterone products used were not reported.

Rhoden and colleagues (106) reported 1 case of prostate cancer in a comparison of intramuscular testosterone (n = 33; dose not reported) and testosterone gel (n = 25; Androgel 1% or Testim 1%, doses not reported). Cohort entry required a negative prostate biopsy before the initiation of testosterone replacement therapy. The group in which the prostate cancer occurred was not reported.

Guay and colleagues (24) reported a retrospective cohort study involving treatment with testosterone enanthate (200–300 mg/2–3 wk), testosterone patch (5 mg/d), or clomiphene citrate. Three cases of prostate cancer were reported; however, to which group the affected patients belonged was not reported, and the duration of follow-up was 2 to 3 months.

SERIOUS ADVERSE EVENTS

Serious adverse events were reported in 2 studies (109, 110) (Table 4.49). Both Francomano and colleagues (110) and Aydogdu and colleagues (109) reported that no serious adverse events occurred during the treatment period in either group.

WITHDRAWALS DUE TO ADVERSE EVENTS

Withdrawals due to adverse events were reported by 3 non-randomized studies (23, 105, 110). Francomano and colleagues (110) and Blick and colleagues both reported zero withdrawals due to adverse events in either study group (Table 4.49). Dean and colleagues reported that 40 participants withdrew from their prospective cohort study (n = 371). However, the authors did not report how many participants were assigned to each treatment group (1% gel 50 mg/d v. 100 mg/d), and they did not report withdrawals by treatment group.

DIABETES

One study reported newly diagnosed diabetes during the treatment period (25). Hijjar and colleagues reported that 1 participant in the testosterone group (intramuscular testosterone enanthate or cypionate) developed diabetes (Table 4.49). However, safety data were provided for only about two-thirds of participants.

HEART DISEASE

No study reported the development of heart disease during the study period.

ERYTHROCYTOSIS

Three studies reported erythrocytosis during the study period (23, 25, 104) (Table 4.49). Blick and colleagues (23) reported that no participant developed erythrocytosis. Aversa and colleagues (104) reported that 4 participant in the testosterone group (n = 40) developed erythrocytosis; zero cases were reported in the control group. Hajjar and colleagues (25) reported that 11 participants in the testosterone group developed erythrocytosis; the authors did not report the occurrence in the control group. Over half of the cases developed during the first year of therapy (25).

SKIN REACTIONS

Skin reactions were mentioned in 4 non-randomized studies (23, 105, 108, 109) (Table 4.49). Aydogdu and colleagues (109) reported that 3 participants in the Sustanon (a blend of testosterone esters administered intramuscularly) group experienced sporadic acne after injection.

Blick and colleagues (23) stated that they assessed skin reactions; however, no data were provided for this outcome.

Dean and colleagues (105) reported that skin reactions were experienced by 5.9% of participants (application site erythema 4%, application site rash 1.9%). In total, 1.1% of participants experienced an application site reaction that led to their withdrawal from the study. All participants in this study were using 1% testosterone gel, at either 50 or 100 mg/d; the number of reactions by treatment group were not reported.

Wang and colleagues (108) reported that 12 participants experienced an application site reaction (11 mild, 1 moderate) and that 1 participant withdrew from the study because of erythema and rash (n = 163). Acne was also reported in 12 participants. All participants in this study were using 1% testosterone gel, at 50, 75, or 100 mg/d. Of the men who experienced an application site reaction, 5 were assigned to the 50 mg/d group, 3 were assigned to the 75 mg/d group, and 4 were assigned to the 100 mg/d group; the total number of men assigned to each group was not reported.

4.4 DISCUSSION

4.4.1 SUMMARY

We performed a comprehensive systematic review of the harms associated with the use of testosterone replacement therapy among hypogonadal men. In our network meta-analysis involving all testosterone replacement therapies reporting each outcome, we found no increased risk of cardiovascular death, myocardial infarction, or serious adverse events. We found that oral testosterone undecanoate was associated with lower odds of prostate cancer compared with testosterone patch or intramuscular enanthate; however, these effects were not seen after adjustment for zero event counts. These findings are based on limited data and require confirmation. Testosterone 1.62% gel was associated with significantly more withdrawals due to adverse events compared with placebo, 1% testosterone gel, or intramuscular testosterone enanthate, and testosterone patch had a higher odds of withdrawals due to adverse events compared with intramuscular testosterone undecanoate. There were limited data for stroke; however, in a pairwise meta-analysis, we found no increased risk of stroke for testosterone compared with placebo.

Although we had intended to incorporate harms data from non-randomized studies of interventions in our meta-analyses, the included studies were generally poorly reported and of poor quality. In particular, the number of participants assigned to each group was frequently not reported, and there were important differences between the treatment groups in some studies. The domains of risks of bias in non-randomized studies are generally similar to those in RCTs, and may be exaggerated by certain study characteristics such as a lack of blinding. Selection bias is of particular concern in non-randomized studies, whereby participants may choose one treatment over another on the basis of a prognostic factor (14). Because of these concerns, we felt that it was not appropriate to perform meta-analysis involving harms data from non-randomized studies; these were summarized narratively.

4.4.2 CONTEXT

In 2014, Health Canada issued a safety alert, based in part on the findings of the Testosterone in Older Men with Mobility Limitations [TOM] trial (3), 2 retrospective cohort

studies (4, 5), and 4 meta-analyses (7, 10, 111, 112), as well as case reports received by Health Canada and other regulators. Of the published studies, the TOM trial, both cohort studies, and 1 meta-analysis (7) reported an increased risk of cardiovascular events among men taking testosterone products. The TOM trial was stopped early by its data safety monitoring board because of an increased number of cardiovascular-related events in the testosterone arm (1% testosterone gel, 100 mg/d) (3). This trial has been criticized for using a broad definition of cardiovascular-related events and because the participants had a high prevalence of comorbidities (including pre-existing hypertension, heart diseases, obesity, diabetes and hypertension). The retrospective cohort study by Vigen and colleagues (4) has also been heavily criticized for poor initial reporting, with calls for its retraction (many of those who called for its retraction had ties to companies that manufacture testosterone products). Despite these perceived flaws, Health Canada and the US Food and Drug Administration deemed the evidence sufficient to issue a warnings about the potential for cardiovascular events among men using these products. In our systematic review and meta-analysis involving only hypogonadal men, we sought to summarize the current evidence for the potential harms associated with the use of testosterone replacement therapy by hypogonadal men.

CARDIOVASCULAR DEATH

Our finding of no increased risk of cardiovascular death is consistent with previous meta-analyses that have reported no increased risk of cardiovascular events (6, 10, 11, 111); however, direct comparison with previous reviews is difficult because most used a composite outcome. One previous review, by Xu and colleagues (7), reported an increased risk of cardiovascular-related events among men taking testosterone replacement therapy; however, they used a composite outcome involving cardiac disorders, cardiovascular complaints, and vascular disorders, while more recent reviews have used a less broad definition of cardiovascular-related events. Most previous reviews have included a heterogeneous population of men with or without low testosterone levels. To the best of our knowledge, this is the first network meta-analysis of the risk of cardiovascular death among hypogonadal men taking testosterone replacement therapy.

MYOCARDIAL INFARCTION

Four previous meta-analyses have assessed the risk of myocardial infarction among men taking testosterone replacement therapy; however, all included both hypogonadal and eugonadal men. Despite this, all found no increased risk of myocardial infarction associated with the use of any testosterone replacement therapy compared with placebo. Each of these previous meta-analyses have compared the risk among men using any testosterone product to the risk among men using placebo.

Our study is the first to compare the risk of myocardial infarction associated with individual testosterone products, using a network meta-analysis design. Among hypogonadal men, we found no increased risk of myocardial infarction associated with any of the testosterone products included in the evidence network. However, data were limited for some treatments, and the data should be interpreted with caution.

Myocardial infarction was reported in 1 non-randomized study, with about 6% of participants in the testosterone group and 2% in the control group experiencing an event. These data were collected as part of composite outcome that used a time-to-event approach; as such, the length of time at risk of an event may have differed between groups, making interpretation of these findings difficult.

STROKE

One previous meta-analysis has assessed the risk of stroke among men taking testosterone replacement therapy (6). Corona and colleagues (6) found no increased risk of stroke among a mixed population of hypogonadal and eugonadal men; our findings among hypogonadal men were consistent with this finding. It should be noted, however, that there were limited data available for this analysis. As such, we were unable to perform network meta-analysis for this outcome, and our findings are based on 3 placebo-controlled trials that reported stroke during the study period, with a total number of events of 3 among 329 men. Two trials each reported 1 stroke in the placebo group, and 1 trial reported 1 stroke in the testosterone group. Of these trials, 2 involved testosterone gel and 1 involved intramuscular testosterone, which represent a small fraction of the total available testosterone products. Our meta-analysis findings of no increased risk of stroke among hypogonadal men enrolled in RCTs

should be interpreted with caution because of the small number of included participants and the small number of testosterone products represented in the analysis.

Stroke was assessed in 1 retrospective cohort study, which reported that about 6% of men in the testosterone group experienced stroke compared with 3% in the comparison group; however, the time at risk may have differed between groups, making interpretation of this finding difficult.

PROSTATE CANCER

The results of previous meta-analyses of the risk of prostate cancer among men taking testosterone replacement therapy have been contradictory. A 2005 meta-analysis involving hypogonadal and eugonadal men reported an increase risk of a composite of prostate-related events among men taking testosterone replacement therapy (10). A 2013 meta-analysis by Fernandez-Balsells and colleagues (11) involving 51 RCTs found no significant difference in the incidence of prostate cancer among hypogonadal and eugonadal men. A 2014 meta-analysis involving 22 randomized controlled trials of up to 36 months duration did not find increased odds of prostate cancer among men with hypogonadism (12). This finding was consistent in studies with a treatment duration of more or less than 1 year and did not differ by route of administration (12). Cui and colleagues (12) also reported no differences in risk depending on the route of administration.

Within one route of administration, however, it is possible to have multiple different testosterone replacement products. For example, the category “topical testosterone products” may include testosterone patch or gel at varying strengths (e.g., 1%, 1.62%, 2%). In our network meta-analysis, we did find no significant difference in the odds of prostate cancer between placebo and any of the included testosterone products. However, we found that oral testosterone undecanoate (160 mg/d) was associated with lower odds of prostate cancer compared with testosterone patch or intramuscular testosterone enanthate. This finding was not conserved after correction of zero events in the network; however, indicating that the limited availability of data is influencing the findings. This finding of increased risk of prostate cancer associated with testosterone patch and intramuscular enanthate compared with oral testosterone undecanoate requires confirmation in a larger study population.

Prostate cancer was the most frequently reported adverse event among the included non-randomized studies. However, because of poor reporting, we were unable to perform pooled analyses.

SERIOUS ADVERSE EVENTS

We found no significant differences in the risk of serious adverse events between placebo and any testosterone replacement therapy or among the therapies included in RCTs. There were no differences in risk by route of administration, treatment duration, or participant age. Whether serious adverse events occurred was not well reported in the included non-randomized studies.

These findings are consistent with previous pairwise meta-analyses that found no significant difference in the odds of a serious adverse event between placebo and testosterone groups.

WITHDRAWALS DUE TO ADVERSE EVENTS

We found that 1.62% testosterone gel was associated with significantly higher odds of withdrawal due to adverse events compared with placebo and compared with 1% gel or intramuscular testosterone undecanoate. We also found that testosterone patch was associated with a higher odds of withdrawal compared with intramuscular testosterone undecanoate. When the treatments were grouped by route of administration, there were no differences between the routes. We found higher odds of withdrawal due to adverse events associated with 1.62% testosterone gel among studies with a treatment duration of 6 months or longer; this treatment was not investigated in any studies with a duration less than 6 months, so we cannot comment on whether the effect varies by treatment duration. To the best of our knowledge, this is the first network meta-analysis to evaluate the odds of withdrawal due to adverse events associated with testosterone replacement products as used by hypogonadal men in RCTs.

Withdrawals due to adverse events were poorly reported in the included non-randomized studies. Two studies reported zero withdrawals (23, 110), while Dean and colleagues reported that about 10% withdrew because of an adverse event (105). In many studies, adverse events occurred but it was unclear whether the participant was withdrawn from the study.

4.4.3 INFLUENCE OF INDUSTRY FUNDING

A 2013 systematic review (7) reported that the odds of a cardiovascular-related event among men taking testosterone replacement therapy differed depending on whether the trial was funded by industry or non-industry sources, with a lower odds reported among industry-funded trials (industry: OR 0.89, 95% CI 0.50 to 1.60; no industry: OR 2.06 1.34 to 3.17). However, this finding was not replicated in a 2014 systematic review involving a similar population (6). However, important differences exist between the 2 analyses, namely the choice of outcome. Xu and colleagues (7) used a broad definition of cardiovascular-related events, which included anything defined by the trial authors as being cardiovascular-related. Corona and colleagues (6) also used a composite outcome for cardiovascular-related events; however, their definition included only cardiovascular death, non-fatal myocardial infarction, stroke, acute coronary syndromes, and heart failure. Corona and colleagues (6) reported no difference in odds of cardiovascular-related events based on the presence (OR 1.07, 95% CI 0.51 to 2.24) or absence (OR 0.94, 0.39 to 2.24) of industry funding.

In the present review, we compared the odds of an event among all studies with the odds of an event among studies that reported no industry funding. Many trials did not report the source of their funding, thus we were unable to directly compare those with or without pharmaceutical funding. There were limited data available from non-industry funded trials, and we were unable to perform network meta-analysis. Based on pairwise meta-analyses, we found similar odds of cardiovascular death, myocardial infarction, stroke, serious adverse events, or withdrawals due to adverse among all trials and those funded by non-industry sources, suggesting that there is not a major influence of industry funding on these outcomes (Table 4.50); however, these comparisons were based on few studies. It is also interesting to note that, despite no significant differences, the point estimates were consistently higher when the analyses were based on studies not funded by industry compared with all studies.

TABLE 4.50: COMPARISON OF HARM OUTCOMES AMONG ALL TRIALS, THOSE WITHOUT INDUSTRY FUNDING, AND THOSE AT LOW RISK OF BIAS

	OR (95% CI); no. of trials contributing data; I^2					
	Cardiovascular death	Myocardial infarction	Stroke	Prostate cancer	Serious adverse events	Withdrawals due to adverse events
All studies	2.49 (0.75 to 8.21); 14; 10%	0.45 (0.14 to 1.50); 10; 41%	0.50 (0.05 to 4.85); 3; 25%	0.78 (0.31 to 1.99); 10; 27%	1.03 (0.66 to 1.61); 11; 4%	1.19 (0.87 to 1.65); 37; 11%
No industry funding	7.18 (0.14 to 362.14); 1; NA	7.25 (0.45 to 116.75); 1; NA	7.18 (0.14 to 365.14); 1; NA	0.99 (0.20 to 4.98); 3; 41%	1.52 (0.71 to 3.28); 2; 54%	1.24 (0.77 to 1.99); 7; 0%
Low overall risk of bias	0.01 (0.00 to 1.41); 1; NA	1.03 (0.16 to 6.68); 3; 5%	NA	0.13 (0.01 to 1.30); 2; 0%	0.47 (95% CI 0.23 to 0.96; 5; 0%	1.18 (0.43 to 3.23); 7; 39%
Note: CI = confidence interval, NA = not applicable, OR = odds ratio.						

4.4.4 PUBLICATION BIAS

Based on visual examination of funnel plots for each outcome, we found no evidence of publication bias for cardiovascular death, myocardial infarction, prostate cancer, serious adverse events, or withdrawals due to adverse events. Although we created a funnel plot for stroke, there were only 4 trials that reported this outcome, making its interpretation difficult. When there are fewer than 10 studies, it is difficult to distinguish between the effects of chance and true asymmetry (14). Publication bias is generally assumed to be absent when the scatter of the effect estimates plotted against the standard error of the estimate forms an inverted funnel shape. If bias is present (e.g., small studies with a significantly increase in the odds of an event remain unpublished), effect estimates will be missing for the bottom right portion of the graph. However, there are additional potential explanations for asymmetry in funnel plots. For example, poor methodological design, inadequate analysis, heterogeneity, or chance can all affect the visual interpretation of funnel plots (14). In our analyses, the funnel plots for each of our harms outcomes appeared to be relatively symmetrical; however, we cannot conclusively rule out the possibility of publication bias.

4.4.5 INFLUENCE OF RISK OF BIAS

In order to assess the harms of testosterone replacement therapy among trials at low risk of bias, we classified trials as being at low, unclear, or high risk based on their score for 3 domains of the Cochrane risk of bias tool (allocation concealment, blinding [subjective outcomes], incomplete data addressed [harms]). When we considered only trials that scored low risk for all 3 of these domains, we found no significant odds of cardiovascular death, myocardial infarction, stroke, prostate cancer, serious adverse events, or withdrawals due to adverse events (Table 4.50). The number of studies at low risk of bias across these 3 domains was a small portion of the total number of studies for each outcome, and additional high-quality studies are needed.

4.4.6 STRENGTHS AND LIMITATIONS

The strengths of our study include a broad, comprehensive search of multiple databases with no language or date restrictions. A separate search of the grey literature was performed. Our systematic review comprehensively summarizes the current evidence of the harms associated with testosterone replacement therapy in men with hypogonadism.

However, there are several limitations that should be considered. First, many of the included studies, both RCTs and non-randomized studies, were small, and the duration was relatively short. This may have limited the ability to detect rare adverse events. For example, stroke was reported by only 4 RCTs, with a total of 3 events. Whether this low event rate is due to a true low incidence or is a result of a short duration of follow-up is unknown.

Second, the quality of the included studies was generally low. The overall risk of bias was generally unclear for most studies, primarily because of unclear or inadequate reporting. For example, over 50% of RCTs were judged to be at high or unclear risk of bias for the domain “incomplete outcome data” for harms outcomes, with high rates of discontinuation that were variable across groups. Of the 11 included non-randomized studies, 6 were deemed to be of unacceptable quality (based on SIGN50 assessment), in part because of unclear reporting of (e.g., number of participants in each group not reported, outcome data not provided for all participants). Because of these issues, we were unable to pool the results from the included non-randomized studies.

Third, although our assessment of publication bias did not indicate that it is a major concern, our analysis was hampered by a lack of data for some outcomes. We assessed publication bias by use of funnel plots, and at least 10 studies are recommended for this analysis. Some outcomes had less than 10 included studies, thus limiting the interpretation of publication bias. In addition, we cannot be assured that selective outcome reporting did not occur, especially among RCTs and non-randomized studies that did not clearly report analysis populations and harms data.

4.4.7 CONCLUSION

In 2014, Health Canada and the US Food and Drug Administration issued warnings about the potential for cardiovascular events among men taking testosterone replacement therapy (113, 114). Our results do not support an increased risk of cardiovascular death, myocardial infarction, or stroke among hypogonadal men using testosterone replacement products; however, this finding is based on low-quality evidence and further long-term high-quality studies are required to confirm the safety of these products.

4.5 REFERENCES

1. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. *Med J Aust* 2013;199(8):548-51.
2. Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.
3. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363(2):109-22.
4. Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829-36.
5. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PloS One* 2014;9(1):e85805, 2014.
6. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014;13(10):1327-51.
7. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013;11:108.
8. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. *Eur Urol* 2006;50(5):935-9.
9. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-59.
10. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 2005;60(11):1451-7.
11. Fernandez-Balsells MM, Murad MH, Lane M, Lampropoulos JF, Albuquerque F, Mullan RJ, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010;95(6):2560-75.
12. Cui Y, Zong H, Yan H, Zhang Y. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2014;17(2):132-43.
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JPA, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 2015;162(11):777-84.
14. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons; 2008.
15. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 2: Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. May 2011. Available: www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf.
16. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, meta-regression, bias and bias-adjustment. May 2011 Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.

17. Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med* 2009;28(14):1861-81.
18. Turner RM, Thompson SG, Spiegelhalter DJ. Prior distributions for the intracluster correlation coefficient, based on multiple previous estimates, and their application in cluster randomized trials. *Clin Trials* 2005;2(2):108-18.
19. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS User Manual. Version 1.42003. Available from: www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual114.pdf.
20. Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. *J Health Serv Res Policy*. 2008;13 Suppl 3:12-22.
21. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004;23(9):1351-75.
22. Morgunov LI, Denisova IA, Rozhkova TI, Stakhovskaia LV, Skvortsova VI. Androgenic deficit and its treatment in stroke male patients with diabetes mellitus type II. *Zh Nevrol Psikhiatr Im S S Korsakova* 2011;111(8 Pt 2):21-4.
23. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. *Postgrad Med* 2013;125(2):30-9.
24. Guay AT, Perez JB, Fitaishi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. *Endocr Pract* 2000;6(2):132-8.
25. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab* 1997;82(11):3793-6.
26. Behre HM, Tammela TL, Arver S, Tolra JR, Bonifacio V, Lamche M, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male* 2012;15(4):198-207.
27. Zhang XW, Liu ZH, Hu XW, Yuan YQ, Bai WJ, Wang XF, et al. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. *Chin Med J* 2012;125(21):3806-10.
28. Ho CCK, Tong SF, Low WY, Ng CJ, Khoo EM, et al. A randomized, double-blind, placebo controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptom Scale. *BJU Int* 2011;110(2):260-265.
29. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011;8(7):2079-89.
30. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 2011;34(4):828-37.
31. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol* 2010;73(5):602-12.
32. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95(2):639-50.

33. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009;54(10):919-27.
34. Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20(4):378-87.
35. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis* 2006;47(2):251-62.
36. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89(2):503-10.
37. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003;6(1):1-7.
38. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl* 1999;22(4):261-5.
39. Schubert M, Minnemann T, Hubler D, Rouskova D, Christoph A, Oettel M, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab* 2004;89(11):5429-34.
40. Ho CC, Tong SF, Low WY, Ng CJ, Khoo EM, Lee VK, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU Int.* 2012;110(2):260-5.
41. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, et al. Efficacy and safety of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011;8(7):2079-2089.
42. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 2010;33(11):776-83.
43. Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;7(10):3495-503.
44. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc* 2010;58(6):1134-43.
45. Sih R, Morley JE, Kaiser FE, Perry HM, III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997;82(6):1661-7.
46. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med* 2013;10(6):1612-27.
47. Shigehara K, Sugimoto K, Konaka H, Iijima M, Fukushima M, Maeda Y, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. *Aging Male* 2011;14(1):53-8.
48. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res* 2009;21(2):129-38.

49. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006;296(19):2351-61.
50. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 2003;88(6):2673-81.
51. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999;84(10):3469-78.
52. Spitzer M, Basaria S, Travison TG, Davda MN, Paley A, Cohen B, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med* 2012;157(10):681-91.
53. Raynaud JP, Legros JJ, Rollet J, Auges M, Bunouf P, Sournac M, et al. Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every 2 days for 1 year to hypogonadal men. *J Steroid Biochem Mol Biol* 2008;109(1-2):168-76.
54. Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 1998;83(9):3155-62.
55. Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, Gouault-Heilmann M, et al. Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care* 2001;24(12):2149-51.
56. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 2008;11(3):140-5.
57. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000;283(6):763-70.
58. Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab*. 2014;306(4):E433-E42.
59. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology* 2004;63(4):641-6.
60. Chiang HS, Cho SL, Lin YC, Hwang TI. Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection: evaluation by IIEF score. *Urology* 2009;73(4):762-6.
61. Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res* 2007;19(4):411-7.
62. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ. Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab* 2003;88(1):358-62.
63. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;129(1):18-26.
64. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control

- in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(6):726-33.
65. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU International* 2003;91(1):69-74.
 66. Merza Z, Blumsohn A, Mah PM, Meads DM, McKenna SP, Wylie K, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl* 2006;29(3):381-91.
 67. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. *Aging Male* 2009;12(4):104-12.
 68. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172(2):658-63.
 69. Shores MM, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J Clin Psychiatry* 2009;70(7):1009-16.
 70. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male* 2003;6(1):13-7.
 71. Kuhnert B, Byrne M, Simoni M, Kopcke W, Gerss J, Lemmnitz G, et al. Testosterone substitution with a new transdermal, hydroalcoholic gel applied to scrotal or non-scrotal skin: a multicentre trial. *Eur J Endocrinol* 2005;153(2):317-26.
 72. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-53.
 73. Nakhai-Pour HR, Grobbee DE, Emmelot-Vonk MH, Bots ML, Verhaar HJ, van der Schouw YT. Oral testosterone supplementation and chronic low-grade inflammation in elderly men: a 26-week randomized, placebo-controlled trial. *Am Heart J* 2007;154(6):1228-7.
 74. Orengo CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. *J Geriatr Psychiatry Neurol* 2005;18(1):20-4.
 75. Kang SM, Jang Y, Kim JY, Chung N, Cho SY, Chae JS, et al. Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. *Am J Cardiol* 2002;89(7):862-864.
 76. Stout M, Tew GA, Doll H, Zwierska I, Woodroffe N, Channer KS, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *Am Heart J* 2012;164(6):893-901.
 77. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol* 2009;161(3):443-9.
 78. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol* 2009;53(8):996-1004.
 79. Yaron M, Greenman Y, Rosenfeld JB, Izkhakov E, Limor R, Osher E, et al. Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. *Eur J Endocrinol*. 2009;160(5):839-46.
 80. Strollo F, Strollo G, More M, Magni P, Macchi C, Masini MA, et al. Low-intermediate dose testosterone replacement therapy by different pharmaceutical preparations improves frailty score in elderly hypogonadal hyperglycaemic patients. *Aging Male* 2013;16(2):33-7.

81. Ross RJM, Siyambalapitiya S, Jonsson P, Koltowska-Haggstrom M, Gaillard R, Ho K. Cross-sectional analysis of testosterone therapies in hypopituitary men on stable pituitary hormone replacement. *Clin Endocrinol* 2009;70(6):907-913.
82. Host C, Bojesen A, Frystyk J, Flyvbjerg A, Christiansen JS, Gravholt CH. Effect of sex hormone treatment on circulating adiponectin and subforms in Turner and Klinefelter syndrome. *Eur J Clin Invest* 2010;40(3):211-219.
83. La VS, Calogero AE, D'Agata R, Di MM, Tumino S, Condorelli R, et al. Testosterone therapy improves the clinical response to conventional treatment for male patients with metabolic syndrome associated to late onset hypogonadism. *Minerva Endocrinologica*. 2008;33(3):159-67.
84. Thomson S, Koren G, Van SV, Rieder M, Van Uum SHM. Testosterone concentrations in hair of hypogonadal men with and without testosterone replacement therapy. *Therapeutic Drug Monitoring* 2009;31(6):779-782.
85. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol* 2005;173(2):533-6.
86. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? *BJU International* 2004;94(7):1066-70.
87. Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E. Prostate volume and growth in testosterone-substituted hypogonadal men are dependent on the CAG repeat polymorphism of the androgen receptor gene: a longitudinal pharmacogenetic study. *J Clin Endocrinol Metab* 2003;88(5):2049-54.
88. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. *Aging Male* 2003;6(2):86-93.
89. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169(6):725-33.
90. Jin B, Conway AJ, Handelsman DJ. Effects of androgen deficiency and replacement on prostate zonal volumes. *Clin Endocrinol* 2001;54(4):437-445.
91. Kalinchenko S, Vishnevskiy EL, Koval AN, Mskhalaya GJ, Saad F. Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: A pilot study. *Aging Male* 2008;11(2):57-61.
92. van den Bergh JP, Hermus AR, Spruyt AI, Sweep CG, Corstens FH, Smals AG. Bone mineral density and quantitative ultrasound parameters in patients with Klinefelter's syndrome after long-term testosterone substitution. *Osteoporos Int* 2001;12(1):55-62.
93. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: Efficacy and treatment cost. *J Sex Med* 2010;7(1 PART 1):269-276.
94. Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology* 2014;83(1):167-73.
95. Arafa M, Zohdy W, Aboulsoud S, Shamloul R. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012;44 Suppl 1:756-63.
96. Gooren LJ, Saad F, Haide A, Yassin A. Decline of plasma 5alpha-dihydrotestosterone (DHT) levels upon testosterone administration to elderly men with subnormal plasma testosterone and high DHT levels. *Andrologia* 2008;40(5):298-302.
97. Kacker R, Connors W, Zade J, Morgentaler A. Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. *J Urology* 2014;191(4):1072-1076.

98. Kubler A, Schulz G, Cordes U, Beyer J, Krause U. The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Exp Clin Endocrinol* 1992;100(3):129-132.
99. La VS, Condorelli R, Vicari E, D'Agata R, Calogero A. Original immunophenotype of blood endothelial progenitor cells and microparticles in patients with isolated arterial erectile dysfunction and late onset hypogonadism: Effects of androgen replacement therapy. *Aging Male* 2011;14(3):183-189.
100. McCullough AR, Khera M, Goldstein I, Hellstrom WJ, Morgentaler A, Levine LA. A multi-institutional observational study of testosterone levels after testosterone pellet (Testopel()) insertion. *J Sex Med* 2012;9(2):594-601.
101. Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. *J Androl* 2008;29(1):102-5.
102. Trabado S, Maione L, Bry-Gauillard H, Affres H, Salenave S, Sarfati J, et al. Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/kallmann syndrome and effects of different modalities of hormonal treatment: A single-center study of 281 patients. *J Clin Endocrinol Metab* 2014;99(2):E268-E275.
103. Trabado S, Maione L, Salenave S, Baron S, Galland F, Bry-Gauillard H, et al. Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities of hormonal treatment. *Fert Steril* 2011;95(7):2324-2329e3.
104. Aversa A, Bruzziches R, Francomano D, Greco EA, Fornari R, Di LL, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. *Aging Male* 2012;15(2):96-102.
105. Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of testim(r) 1% testosterone gel in hypogonadal men. *Rev Urol* 2005;7(2):87-94.
106. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. *Int J Impot Res* 2006;18(2):201-205.
107. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97(6):2050-8.
108. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 2004;89(5):2085-98.
109. Aydogdu A, Bolu E, Sonmez A, Tasci I, Haymana C, Acar R, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clin Endocrinol* 2013;9(2):243-251.
110. Francomano D, Bruzziches R, Barbaro G, Lenzi A, Aversa A. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: A pilot study. *J Endocrinol Invest* 2014;37(4):401-411.
111. Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82(1):29-39.
112. Fernandez-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, et al. Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010;95(6):2560-2575.

113. Canada H. Information update: Possible cardiovascular problems associated with testosterone products 2014 [cited April 15, 2015]. Available: www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/40587a-eng.php.
114. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. 2015 [cited May 11, 2015]. Available: www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf.

CHAPTER 5: SUMMARY AND FUTURE DIRECTIONS

5.1 SUMMARY

Despite over 70 years of use, the efficacy and safety of testosterone replacement therapies has not been convincingly established. The results of the Testosterone in Older Men (TOM) trial and of several observational studies have suggested that there may be an increased risk of adverse cardiovascular events associated with testosterone replacement therapy; however, the results of previous meta-analyses have been inconsistent.

We undertook this systematic review and meta-analysis to summarize the current evidence for the benefits and harms associated with the use of testosterone replacement therapy among hypogonadal men. In contrast with previous reviews, we included only randomized controlled trials (RCTs) and non-randomized studies of interventions that enrolled hypogonadal men because this is the population for whom these agents are approved by Health Canada and the United States Food and Drug Administration. We found that 3 testosterone products improved depressive symptoms and that 1 product improved quality of life (Table 5.1). There were no significant differences for erectile function or libido. We found no increased risk of cardiovascular death, myocardial infarction, stroke, or serious adverse events among men undergoing testosterone replacement therapy, although the odds of prostate cancer and withdrawals due to adverse events varied by product.

In contrast with previous reviews, we used a network meta-analysis approach to allow comparison of treatments that have never been compared in head-to-head trials. This approach also allows comparison of each individual testosterone replacement product with placebo, whereas previous meta-analyses have compared placebo with any testosterone product as a group. Our finding for the benefits of testosterone replacement therapy are generally consistent with previous reviews, although we extended previous analyses to compare testosterone therapies with each other instead of just with placebo. The findings from our analysis of the harms associated with testosterone replacement products were generally similar to most previous meta-analyses. Of the 4 available meta-analyses of cardiovascular-related events, only 1 reported an increased risk associated with the use of

testosterone replacement therapy (1); however, this meta-analysis has been criticized because of the inclusion of events not typically included in composite cardiovascular outcomes (e.g., peripheral edema, self-reported syncope) (2). Previous meta-analyses have also included both hypogonadal and eugonadal men.

TABLE 5.1: SUMMARY OF MAIN FINDINGS

Outcome	No. treatments in network	Number of participants (RCTs)	Baseline rate (placebo group)	NMA finding (primary analysis)	Low risk of bias (sensitivity analysis)	Comments
Depression	10	1057 (12)	NA	- Oral TU (T-based dose, 160 mg/d) and IM TE (200 mg/2 wk) improved symptoms of depression v. placebo - Oral TU better than most other products	3 of 12 trials at low ROB - No difference in efficacy when only trials at low ROB included	Treatments for which a significant difference was found in the primary analysis were from trials at high ROB; no difference when low ROB trials were considered
Quality of life	14	2610 (20)	NA	- Oral TU (T-based dose) improved quality of life relative to placebo - No differences among TRTs	9 of 20 trials at low ROB - Patch (5 mg/d) improved QoL relative to placebo, 1% gel (100 mg/d) and oral TU (160 mg/d)	When only low ROB studies were included, patch was superior to other TRTs. Treatment that was significant in primary analysis was from one trial at high ROB
Erectile function	5	1138 (10)	NA	No differences in erectile function relative to placebo or among TRTs	5 of trials at low ROB - No differences in erectile function relative to placebo or among the treatments (3 treatments)	Findings consistent between primary analysis and studies at low ROB
Libido	7	1631 (10)	NA	No differences in libido relative to placebo or among TRTs	3 trials at low ROB - No differences in libido relative to placebo or among the treatments	
Testosterone level (end of study)	25	46	NA	11 treatments improved total T relative to placebo 2% gel, IM TE better than most other products	NA	Most treatments were associated with normal (> 12 nmol/L) total T levels at end of study
CV death	9	2101 (15)	1.64%	No differences in odds of CV death relative to placebo or among TRTs	3 trials at low ROB - MA: no increased risk for any TRT v. placebo	Analysis based on few events; wide CrI
Myocardial infarction	8	1562 (10)	2.13%	No differences in odds of MI relative to placebo or among TRTs	3 trials at low ROB - MA: no increased odds for any TRT v. placebo	Analysis based on few events; wide CrI
Stroke	NA	329 (4)	NA	- No network possible - No increased odds of stroke in MA (any	No trials at low ROB	Very limited data

Outcome	No. treatments in network	Number of participants (RCTs)	Baseline rate (placebo group)	NMA finding (primary analysis)	Low risk of bias (sensitivity analysis)	Comments
TRT v. placebo)						
Prostate cancer	9	2028 (11)	1.71%	No increased odds with any TRT after continuity correction	2 trials at low ROB - MA: no increased risk for any TRT v. placebo	Oral TU had lower odds of PCa compared with some other TRTs in base analysis (no adjustment); differences were not conserved after adjustment for zero events; wide CrI
Serious adverse events	9	2184 (13)	4.57%	No increased odds with any TRT	5 trials at low ROB - MA: lower odds of SAE in TRT group; OR 0.47 (95% CI 0.23-0.96; $I^2 = 0\%$)	Wide CrI in network for some treatments with limited data.
Withdrawals due to adverse events	21	3834 (70)	5.26%	1.62% gel had higher odds of WAE compared with placebo and 1% gel	8 trials at low ROB - MA: no increased odds for any TRT v. placebo	
Note: CI = confidence interval, IM = intramuscular, MA = meta-analysis, MI = myocardial infarction, NA = not applicable, OR = odds ratio, PCa = prostate cancer, ROB = risk of bias, SAE = serious adverse events, T = testosterone, TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate, WAE = withdrawal due to adverse events.						

Our finding of increased risk of prostate cancer associated with some testosterone replacement therapies in our primary analysis was unexpected. However, because of a large number of zero event counts in the network, the estimates were not robust. After correction for these zero counts, there were no significant differences between products. The most recent systematic review to evaluate the odds of prostate cancer among hypogonadal men enrolled in placebo-controlled RCTs found no increased risk compared with placebo; our adjusted results are consistent with this finding.

Although we had intended to incorporate the results of non-randomized studies into our meta-analysis of harms, the included studies were generally poorly reported and of poor quality, making their interpretation difficult. Because of these concerns, we felt that it was not appropriate to combine the results from the included randomized and non-randomized studies.

5.2 CLINICAL IMPORTANCE

In this systematic review, the focus has been largely on statistical significance. However, clinical importance should also be considered in patient care. While a result may be statistically significant, it may not be clinically important, and, conversely, a non-statistically significant result may be clinically important (3). One factor in making such a determination is the minimal clinically important difference (MCID), or the smallest difference in treatment efficacy that would make a difference in patient care, given potential harms, costs and inconvenience of a therapy (3).

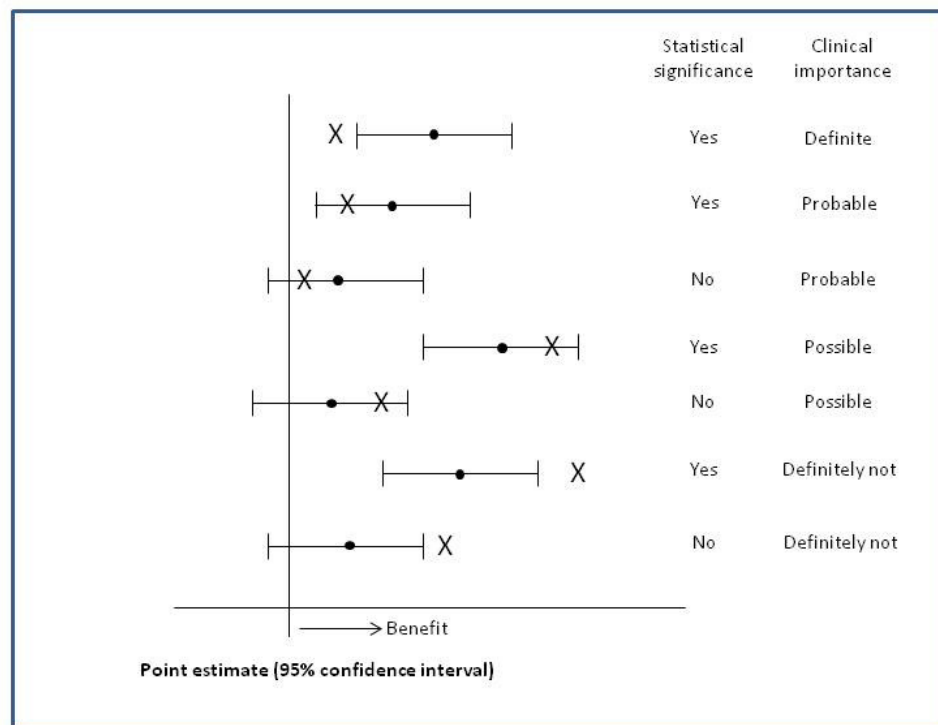
In contrast to determining statistical significance, determining clinical importance is not as clear. Although the MCID should be defined a priori (and be used in sample size calculations), MCIDs in clinical trials are often chosen from convenience to achieve a feasible sample size (3). Others may take expert opinion or patient perspectives into account when determining the MCID. If known, the MCID can be used in the determination of clinical significance.

In order to assess the clinical importance of testosterone replacement therapy, we compared the MCID with the point estimates and credible intervals, following the general criteria proposed by Man-Son-Hing and colleagues (3). Man-Son-Hing proposed 4 main categories of clinical importance: definite, probable, possible, and definitely not (Figure 5.1). Under this categorization system, treatments that have a point estimate and lower limit of the 95% confidence (or credible) interval above the MCID can be said to have definite clinical importance, while treatments that have a point estimate and upper limit below the MCID are said to have definitely no clinical importance. Probable and possible clinical importance lie between these extremes; the distinction relates to the position of the point estimate relative to the MCID (Figure 5.1).

5.2.1 DEPRESSION

Of the studies that assessed depression, none reported the MCID. However, the National Institute for Clinical Excellence suggests that a difference of 3 or more points on the Beck Depression Inventory (BDI) is clinically important (4). To compare our results with this

FIGURE 5.1: RELATION BETWEEN STATISTICAL SIGNIFICANCE AND CLINICAL IMPORTANCE. ADAPTED FROM MAN-SON-HING 2002 (3). "X" INDICATES THE MINIMUM CLINICALLY IMPORTANT DIFFERENCE



threshold, standardized mean differences were converted to a score on the BDI by multiplying the standardized mean difference by the baseline standard deviation of a representative trial (5). Of the treatments involved in the network, only 2 resulted in a mean difference of more than 3 points on the BDI, suggesting a probable clinically important difference following testosterone treatment (Table 5.2). Both of these treatments (oral TU 120-160 mg/d, oral TU 160 mg/d) were also statistically significant. One treatment, which was found to have a statistically significant effect on depression in the network meta-analysis (IM TE 200 mg/2 wk) was classified as having a possible clinical important effect. The remaining treatments were all classified as having definitely no clinical importance.

TABLE 5.2: COMPARISON OF STATISTICAL SIGNIFICANCE AND CLINICAL IMPORTANCE

Outcome	MCID (scale)	No. of treatments in network	Statistically significant (v. placebo)	Clinical importance
Depression	3 points (BDI)	10	3	Definite: 0 Probable: 2 Possible: 2 Definitely not: 6
Quality of life	4.64 points (AMS)	14	1	Definite: 0 Probable: 3 Possible: 11 Definitely not: 0
Erectile function	4 points (IIEF-EF)	5	0	Definite: 0 Probable: 2 Possible: 2 Definitely not: 6
Libido	Unknown	7	0	Small: 5 Moderate: 1 Large: 1
Note: AMS = Aging Males Symptoms scale, BDI = Beck Depression Inventory, IIEF-EF= International Index of Erectile Function, erectile function domain, MCID = minimum clinically important difference.				

5.2.2 QUALITY OF LIFE

Of the trials that assessed quality of life, only 1 reported an MCID (6). Ho and colleagues (6) assessed quality of life using the Aging Males' Symptoms (AMS) scale, and stated that the MCID was a decrease of 4.64 points. After conversion of the standardized mean difference values to scores on the AMS scale (7), the scores ranged from a reduction of 18 points to an increase of 4 points relative to placebo. The 1 treatment that was statistically significant compared with placebo (oral testosterone undecanoate, weight-based dose) had a decrease of 18 points on the AMS scale compared with placebo and was classified as having probable clinical importance (Table 5.2). Two other treatments were also classified as having probable clinical importance based on the point estimate being greater than the MCID. Of the remaining trials, 11 were classified as having possible clinical importance, and none were considered to have definitely no clinical importance.

5.2.3 ERECTILE FUNCTION

Of the trials included in the network, none reported an MCID for erectile function. All trials assessed erectile function using 1 of 2 versions of the International Index of Erectile Function (IIEF). An MCID of 4 points has been suggested to be clinically important (8) for the erectile function domain of the IIEF. When the standardized mean difference estimates from our network meta-analysis were converted to mean differences on this scale, all 5 treatments were associated with a possible clinically important effect (Table 5.2). None had a definite, probable, or definitely no clinical effect.

5.2.4 LIBIDO

Of the 10 trials included in the network meta-analysis of libido, none reported an MCID, and, to the best of our knowledge, an MCID has not been calculated for any of the scales involved in this network. Using the ‘rule of thumb’ proposed by Cochrane for interpreting effect sizes (9), standardized mean differences above 0.7 can be considered to have a large effect, while those between 0.4 and 0.7 have a moderate effect, and those below 0.4 have a small effect. Of the treatments included in this network, only 1 was associated with an standardized mean difference above 0.8 (oral TU 160 mg/d); 1 had a difference between 0.4 and 0.7 (oral TU 120 mg/d), and 5 had a difference below 0.4 (Table 5.2).

Although for most treatments statistical significance was not reached, many were associated with possible or probable clinical importance. This highlights the importance of considering clinical importance as well as statistical significance when discussing efficacy, and is generally in keeping with the recommendations by the Endocrine Society to provide “testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at ...improving their sexual function, [and] sense of well-being...” (10).

5.3 FUTURE DIRECTIONS

Our systematic review and analysis focused on hypogonadal men. Although this is the group for whom these agents are approved, hypogonadal men may comprise a small portion of the men actually taking testosterone replacement products. In a recent database study in Ontario of men aged 66 years and older, only about 6% of men who started taking a testosterone

replacement product had a recorded diagnosis of hypogonadism (11). A future review of the harms associated with testosterone replacement products should include studies involving both hypogonadal and eugonadal men to provide an estimate of risk among the population taking these agents.

A vast body of non-comparative observational studies of testosterone replacement therapy exists. These studies were excluded from the present analysis because we sought to include only evidence from comparable groups. Traditional meta-analysis and network meta-analysis are based on the presence of at least 2 comparative groups; however, new methods are being developed to allow the inclusion of single-arm studies in networks alongside traditional data from RCTs (12). It may be possible in a future systematic review to synthesize all available evidence from both observational and randomized studies; however, the quality of data from non-randomized studies may be a limiting factor.

5.4 IMPLICATIONS FOR PRACTICE

We found little statistical benefit associated with the use of testosterone replacement therapy; however, some of the testosterone products may be associated with clinical improvement. Although we did not find increased risk of major harms, we cannot rule out the possibility of major harm because of the low quality of the evidence, the rare nature of these events, and the short duration of treatment in the included studies. Until additional long-term high-quality studies that evaluate adverse events as pre-specified outcomes are available, men with late-onset hypogonadism may choose to avoid testosterone replacement products or to weigh the potential harms with the lack of benefit for most outcomes.

5.4 REFERENCES

1. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013;11:108.
2. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014;13(10):1327-51.
3. Man-Son-Hing M, Laupacis A, O'Rourke K, Molnar FJ, Mahon J, Chan KB, et al. Determination of the clinical importance of study results. *Journal of general internal medicine*. 2002;17(6):469-76.
4. Health NCCfM. Depression: Management of Depression in Primary and Secondary Care. Leicester and London: : National Institute for Clinical Excellence, 2004.
5. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *Journal of Clinical Endocrinology and Metabolism*. 2004;89(2):503-10.
6. Ho CC, Tong SF, Low WY, Ng CJ, Khoo EM, Lee VK, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU International*. 2012;110(2):260-5.
7. Behre HM, Tammela TL, Arver S, Tolra JR, Bonifacio V, Lamche M, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male*. 2012;15(4):198-207.
8. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. *Eur Urol*. 2011;60(5):1010-6.
9. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons; 2008.
10. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2010;95(6):2536-59.
11. Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PloS One* 2014;9(7):e98003.
12. Thom HH, Capkun G, Cerulli A, Nixon RM, Howard LS. Network meta-analysis combining individual patient and aggregate data from a mixture of study designs with an application to pulmonary arterial hypertension. *BMC Med Res Methodol* 2015;15:34.

APPENDIX 1: DETAILED LITERATURE SEARCH STRATEGY

Testosterone Replacement Therapy
Primary Studies - Final Strategies
2014 Jun 3

Database: Embase Classic+Embase <1947 to 2014 June 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

- 1 exp Testosterone/aa, ad, ae, tu (9143)
- 2 Testosterone Congeners/ad, ae, tu (391)
- 3 exp Testosterone/ and Hormone Replacement Therapy/ (4361)
- 4 exp Androgens/ and Hormone Replacement Therapy/ (5792)
- 5 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream\$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
- 6 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream\$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
- 7 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
- 8 TRT.tw. (2125)
- 9 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
- 10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
- 11 ("Bio-T-Gel" or Ciclosteroone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
- 12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
- 13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon\$1 or "Sustason 250" or Synandrol).tw. (674)
- 14 (Teslen or "Testa-C" or Testamone or Testandron or Testaqua or Testosterone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
- 15 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
- 16 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
- 17 or/1-16 (39453)
- 18 exp Animals/ not (exp Animals/ and Humans/) (8702141)
- 19 17 not 18 (25517)
- 20 (controlled clinical trial or randomized controlled trial).pt. (457659)
- 21 clinical trials as topic.sh. (169995)
- 22 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1423548)
- 23 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
- 24 trial.ti. (292735)
- 25 or/20-24 (1829141)
- 26 19 and 25 (3594)
- 27 (comment or editorial or interview or letter or news).pt. (2802584)
- 28 26 not 27 (3546)
- 29 (control* adj2 trial*).tw. (323672)
- 30 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
- 31 (nRCT or nRCTs or non-RCT\$1).tw. (647)
- 32 (control* adj3 ("before and after" or "before after")).tw. (6046)
- 33 time series.tw. (33994)
- 34 (pre- adj3 post-).tw. (110642)
- 35 (pretest adj3 posttest).tw. (6260)
- 36 (control* adj2 stud\$3).tw. (346641)
- 37 Control Groups/ (74764)
- 38 (control\$ adj2 group\$1).tw. (752277)
- 39 or/29-38 (1509227)
- 40 19 and 39 (2115)
- 41 40 not 27 (2097)
- 42 exp Cohort Studies/ (1517558)
- 43 cohort\$1.tw. (675350)
- 44 Retrospective Studies/ (837256)

45 (longitudinal or prospective or retrospective).tw. (1721897)
 46 ((followup or follow-up) adj (study or studies)).tw. (89267)
 47 Observational study.pt. (2469)
 48 (observation\$2 adj (study or studies)).tw. (111012)
 49 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
 50 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
 51 Comparative Study.pt. (1676994)
 52 ((comparative or comparison) adj (study or studies)).tw. (185742)
 53 or/42-52 (4729450)
 54 19 and 53 (3389)
 55 54 not 27 (3352)
 56 28 or 41 or 55 (6587)
 57 56 use prnz (3219) [ALL MEDLINE RECORDS]
 58 28 use prnz (1720) [MEDLINE RCTS]
 59 41 use prnz (845) [MEDLINE NON-RCTS]
 60 55 use prnz (1837) [MEDLINE OBSERV]
 61 androgen therapy/ (3539)
 62 androgen deficiency/dt (507)
 63 testosterone undecanoate/ (1591)
 64 testosterone cypionate/ (871)
 65 testosterone enantate/ (2439)
 66 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream\$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
 67 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream\$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
 68 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
 69 TRT.tw. (2125)
 70 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cypionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
 71 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
 72 ("Bio-T-Gel" or Ciclosteroone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
 73 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oretone or "Oretone-F" or Orquisteron).tw. (292)
 74 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primotestone or Relibra or Restandol or Sterotate or Striant or Sustanon\$1 or "Sustason 250" or Synandrol).tw. (674)
 75 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropion or Testosteroid).tw. (691)
 76 (Testosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
 77 (UNII-3XMK78S47O or Undestor or Virilon or Viormone or Virosterone or Vogelxo).tw. (61)
 78 or/61-77 (33099)
 79 randomized controlled trial/ or controlled clinical trial/ (936519)
 80 exp "clinical trial (topic)"/ (104828)
 81 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1423548)
 82 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
 83 trial.ti. (292735)
 84 or/79-83 (1962147)
 85 78 and 84 (4042)
 86 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37422531)
 87 exp humans/ or exp human experimentation/ or exp human experiment/ (28425359)
 88 86 not 87 (8998814)
 89 85 not 88 (3544)
 90 (letter or editorial).pt. (2492646)
 91 89 not 90 (3515)
 92 (control* adj2 trial*).tw. (323672)
 93 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
 94 (nRCT or nRCTs or non-RCT\$1).tw. (647)
 95 (control* adj3 ("before and after" or "before after")).tw. (6046)
 96 time series analysis/ (13996)
 97 time series.tw. (33994)
 98 pretest posttest control group design/ (202)
 99 (pre- adj3 post-).tw. (110642)

100 (pretest adj3 posttest).tw. (6260)
 101 controlled study/ (4336835)
 102 (control* adj2 stud\$3).tw. (346641)
 103 control group/ (74764)
 104 (control* adj2 group\$1).tw. (752277)
 105 or/92-104 (5430128)
 106 78 and 105 (7057)
 107 106 not 88 (3849)
 108 107 not 90 (3833)
 109 cohort analysis/ (334727)
 110 cohort\$1.tw. (675350)
 111 retrospective study/ (837256)
 112 longitudinal study/ (153245)
 113 prospective study/ (618128)
 114 (longitudinal or prospective or retrospective).tw. (1721897)
 115 follow up/ (824941)
 116 ((followup or follow-up) adj (study or studies)).tw. (89267)
 117 observational study/ (58475)
 118 (observation\$2 adj (study or studies)).tw. (111012)
 119 population research/ (68859)
 120 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
 121 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
 122 exp comparative study/ (2694962)
 123 ((comparative or comparison) adj (study or studies)).tw. (185742)
 124 or/109-123 (5973302)
 125 78 and 124 (4650)
 126 125 not 88 (3667)
 127 126 not 90 (3625)
 128 91 or 108 or 127 (7409)
 129 128 use emczd (5052) [ALL EMBASE RECORDS]
 130 91 use emczd (2221) [EMBASE RCTS]
 131 108 use emczd (3091) [EMBASE NON-RCTS]
 132 127 use emczd (2341) [EMBASE OBSERV]
 133 58 or 130 (3941) [MEDLINE/EMBASE RCTS]
 134 remove duplicates from 133 (2771) [UNIQUE RCTS]
 135 134 use prmz (1666) [MEDLINE UNIQUE RCTS]
 136 134 use emczd (1105) [EMBASE UNIQUE RCTS]
 137 59 or 131 (3936) [MEDLINE/EMBASE NON-RCTS]
 138 137 not 133 (1817) [OVERLAP REMOVED]
 139 remove duplicates from 138 (1633) [UNIQUE NON-RCTS]
 140 139 use prmz (264) [MEDLINE UNIQUE NON-RCTS]
 141 139 use emczd (1369) [EMBASE UNIQUE NON-RCTS]
 142 60 or 132 (4178) [MEDLINE/EMBASE OBSERV]
 143 142 not (133 or 137) (2513) [OVERLAP REMOVED]
 144 remove duplicates from 143 (2170) [UNIQUE OBSERV]
 145 144 use prmz (1216) [MEDLINE UNIQUE OBSERV STUDIES]
 146 144 use emczd (954) [EMBASE UNIQUE OBSERV STUDIES]
 147 134 or 139 or 144 (6574) [UNIQUE RECORDS – ALL STUDY TYPES]

Cochrane Library

Search Name: Testosterone Replacement Therapy
 Date Run: 03/06/14 16:19:59.596
 Description: Ottawa Heart Institute - 2014 Jun 3

ID	Search	Hits
#1	[mh Testosterone/aa,ad,ae,tu]	733
#2	[mh ^"Testosterone Congeners"/ad,ae,tu]	23
#3	[mh Testosterone] and [mh "Hormone Replacement Therapy"]	176
#4	[mh Androgens] and [mh "Hormone Replacement Therapy"]	54
#5	(testosteron* near/3 (replac* or substitut* or supplement* or therap* or treatment* or buccal* or cream* or gel or gels or implant* or inject* or oral* or patch* or transdermal*)) :ti,ab,kw	1080
#6	(androgen* near/3 (replac* or substitut* or supplement* or therap* or treatment* or cream* or gel or gels or implant* or inject* or patch*)) :ti,ab,kw	956

#7 (androgen* near/3 (buccal* or oral* or transdermal*)):ti,ab,kw 116

#8 TRT:ti,ab,kw 131

#9 (testosterone next (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")):ti,ab,kw 291

#10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron):ti,ab,kw 36

#11 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatesteryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate):ti,ab,kw 11

#12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oretone or "Oretone-F" or Orquisteron):ti,ab,kw 5

#13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon\$1 or "Sustason 250" or Synandrol):ti,ab,kw 3

#14 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testosterone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid):ti,ab,kw 16

#15 (Testosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or "Trans-Testosterone"):ti,ab,kw 10

#16 (UNII-3XMK78S47O or Undestor or Virilon or Viormone or Viosterone or Vogelxo):ti,ab,kw 1

#17 {or #1-#16} 2359

DSR – 35 (*did not download*)

DARE – 49 (*did not download*)

CENTRAL – 2258

Methods – 2 (*did not download*)

HTA – 3 (*did not download*)

NHS EED – 12 (*did not download*)

APPENDIX 2: LIST OF INCLUDED STUDIES (RANDOMIZED AND NON-RANDOMIZED)

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol*. 2005;173(2):533-536.
2. Agledahl I, Brodin E, Svartberg J, et al. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombo Haemostasis*. 2009;102:945.
3. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008;68:641.
4. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab*. 2004;89(2):503-510.
5. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol*. 2009;53(8):996-1004.
6. Arafa M, Zohdy W, Aboulsoud S, et al. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012;44 (Suppl 1):756.
7. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. *J Androl*. 1999;20(5):611-618.
8. Atkinson RA, Srinivas-Shankar U, Roberts SA, et al. Effects of testosterone on skeletal muscle architecture in intermediate-frail and frail elderly men. *J Gerontol A Biol Sci Med Sci* 2010;65:1215.
9. Aversa A, Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 36 months controlled study. *Aging Male* 2012;15:96.
10. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;7:3495.
11. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33(11):776-783.
12. Aydogdu A, Bolu E, Sonmez A, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clin Endocrinol* 2013;79(2):243-51.
13. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci*. 2014;69(6):725-735.
14. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-122.
15. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci*. 2013;68(2):153-160.
16. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male*. 2008;11(3):140-145.
17. Behre HM, Tammela TL, Arver S., et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male* 2012;15:198.
18. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000;283(6):763-770.
19. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab*. 1998;83(9):3155-3162.
20. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: Can a case be made for a 3-month therapeutic trial? *BJU International*. 2004;94(7):1066-1070.
21. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. *Postgrad Med*. 2013;125(2):30-39.
22. Borst SE, Yarrow JF, Conover CF, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab* 2014;306(4):E433-E442.
23. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male*. 2003;6(1):1-7.

24. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis.* 2006;47(2):251-262.
25. Buisson J. Effects of testosterone supplementation on sexual function in elderly men: Results of a six month randomised, placebo controlled study. *Cahiers de l'Annee Gerontologique* 2010;2(3):144-6.
26. Burnett AL, Kan-Dobrosky N, Miller MG. Testosterone replacement with 1% testosterone gel and priapism: no definite risk relationship. *J Sex Med.* 2013;10(4):1151-1161.
27. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *J Am College Cardiol* 2009;54:919.
28. Cavallini G, Biagiotti G, Giudice C. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 2012;33:381.
29. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology.* 2004;63(4):641-6.
30. Chiang HS, Cho SL, Lin YC, Hwang TI. Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection: evaluation by IIEF score. *Urology.* 2009;73(4):762-766.
31. Chiang HS, Hwang TI, Hsui YS, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res.* 2007;19(4):411-417.
32. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl.* 1999;22(4):261-265.
33. Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of Testim 1% testosterone gel in hypogonadal men. *Rev Urol* 2005;7(2):87-94.
34. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab.* 1999;84(10):3469-3478.
35. Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I, Rudman D. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *J Am Geriatr Soc.* 1995;43(8):899-901.
36. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA* 2008;299(1):39-52.
37. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res.* 2009;21(2):129-38.
38. Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clin Endocrinol* 2010;73:102.
39. Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol.Endocrinol.Metab.* 2002;282(3):E601-E607.
40. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ. Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab.* 2003;88(1):358-362.
41. Francomano D, Ilacqua A, Bruzziches R, et al. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology* 2014;83:167.
42. Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol* 2014;2014:527470.
43. Francomano D, Bruzziches R, Barbaro G, et al. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: A pilot study. *J Endocrinol Invest* 2014;37(4):401-11.
44. Giltay EJ, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med* 2010;7:2572.
45. Gooren LJ, Saad F, Haide A, et al. Decline of plasma 5alpha-dihydrotestosterone (DHT) levels upon testosterone administration to elderly men with subnormal plasma testosterone and high DHT levels. *Andrologia* 2008;40:298.
46. Gopal RA, Bothra N, Acharya SV, et al. Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus. *Endocr Pract* 2010;16:570-6.
47. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1998;129(1):18-26.
48. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab.* 2000;85(1):60-65.
49. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. *Endocr Pract.* 2000;6(2):132-138.
50. Hackett G, Cole N, Bhartia M, et al; BLAST Study Group. The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). *Int J Clin Pract* 2014;68:203.
51. Hackett G, Cole N, Bhartia M et al; BLAST Study Group. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. *J Sex Med* 2014;11:840.

52. Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med* 2013;10:1612.
53. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab*. 1997;82(11):3793-3796.
54. Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990;71:216.
55. Heufelder AE, Saad F, Bunck MC, et al. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30:726.
56. Hildreth KL, Barry DW, Moreau KL, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. *J Clin Endocrinol Metab*. 2013;98(5):1891-1900.
57. Ho CC, Tong SF, Low WY, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU Int* 2012;110:260.
58. Hohl A, Marques MO, MH Coral, et al. Evaluation of late-onset hypogonadism (andropause) treatment using three different formulations of injectable testosterone. *Arq Bras Endocrinol Metabol* 2009;53:989.
59. Host C, Bojesen A, Frystyk J, Flyvbjerg A, Christiansen JS, Gravholt CH. Effect of sex hormone treatment on circulating adiponectin and subforms in Turner and Klinefelter syndrome. *Eur J Clin Invest* 2010;40(3):211-9.
60. Huang G, Bhasin S, Tang ER, et al. Effect of testosterone administration on liver fat in older men with mobility limitation: results from a randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2013;68(8):954-9.
61. Jin B, Conway AJ, Handelsman DJ. Effects of androgen deficiency and replacement on prostate zonal volumes. *Clinical Endocrinology* 2001;54(4): 437-445.
62. Jockenhovel F, Bullmann C, Schubert M, et al. Influence of various modes of androgen substitution on serum lipids and lipoproteins in hypogonadal men. *Metabolism* 1999;48:590.
63. Jockenhovel F, Vogel E, Reinhardt W, et al. Effects of various modes of androgen substitution therapy on erythropoiesis. *Euro J Med Res* 1997;2:293.
64. Jockenhovel F, Minnemann T, Schubert M, et al. Timetable of effects of testosterone administration to hypogonadal men on variables of sex and mood. *Aging Male* 2009;12:113.
65. Jockenhovel F, Minnemann T, Schubert M, et al. Comparison of long-acting testosterone undecanoate formulation versus testosterone enanthate on sexual function and mood in hypogonadal men. *Eur J Endocrinol* 2009;160:815.
66. Jockenhovel F, Blum WF, Vogel E, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endo Metabo* 1997;82:2510.
67. Jones TH, Arver S, Behre HM, et al. Channer, TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 2011;34:828.
68. Kacker R, Connors W, Zade J, et al. Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. *J Urology* 2014;191(4):1072-6.
69. Kalinchenko S, Vishnevskiy EL, Koval AN, Mskhalaya GJ, Saad F. Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: A pilot study. *Aging Male*. 2008;11(2):57-61.
70. Kalinchenko SY, Tishova Y.A, Mskhalaya GJ, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol* 2010;73:602.
71. Kang SM, Jang Y, Kim JY, et al. Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. *Am J Cardiol* 2002;89(7):862-4.
72. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 2006;154:899.
73. Kapoor D, Clarke S, Stanworth R., et al. The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 2007;156:595-602.
74. Kaufman JM, Miller MG, Garwin JL, et al. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011;8:2079.
75. Kenny AM, Kleppinger A, Annis K, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc*. 2010;58(6):1134-1143.
76. Kubler A, Schulz G, Cordes U, et al. The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Exp Clin Endocrinol* 1992;100(3):129-32.
77. Kuhnert B, Byrne M, Simoni M, et al. Testosterone substitution with a new transdermal, hydroalcoholic gel applied to scrotal or non-scrotal skin: a multicentre trial. *Eur J Endocrinol* 2005;153:317.
78. Lu J, Fan J, Zhu J, et al. The prospective and randomized control study of Viagra combined with Andriol in the treatment of ED in the aging male. *Chinese J Androl* 2003;17:194.
79. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006;296(19):2351-2361.

80. Mathur A, Malkin C, Saeed B, et al. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol* 2009;161:443.
81. McCullough AR, Khera M, Goldstein I, et al. A multi-institutional observational study of testosterone levels after testosterone pellet (Testopel) insertion. *J Sex Med* 2012;9:594.
82. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU International*. 2003;91(1):69-74.
83. Merza Z, Blumsohn A, Mah PM, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl* 2006;29:381.
84. Minnemann T, Schubert M, Freude S, et al. Comparison of a new long-acting testosterone undecanoate formulation vs testosterone enanthate for intramuscular androgen therapy in male hypogonadism. *J Endocrinol Invest* 2008;31:718.
85. Montano M, Flanagan JN, Jiang L, et al. Transcriptional profiling of testosterone-regulated genes in the skeletal muscle of human immunodeficiency virus-infected men experiencing weight loss. *J Clin Endocrinol Metab*. 2007;92(7):2793-2802.
86. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. *Aging Male*. 2009;12(4):104-112.
87. Morgunov LI, Denisova IA, Rozhkova TI, et al. Androgenic deficit and its treatment in stroke male patients with diabetes mellitus type II. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2011;111:21.
88. Muraliedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169(6):725-733.
89. Nakhai-Pour HR, Grobbee DE, Emmelot-Vonk MH, Bots ML, Verhaar HJ, van der Schouw YT. Oral testosterone supplementation and chronic low-grade inflammation in elderly men: a 26-week randomized, placebo-controlled trial. *Am Heart J*. 2007;154(6):1228.
90. O'Connell MD, Roberts SA, Srinivas-Shankar U, et al. Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? *J Clin Endocrinol Metab* 2011;96:454.
91. Orengo CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. *J Geriatr Psychiatry Neurol*. 2005;18(1):20-4.
92. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab*. 2005;90(3):1502-10.
93. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. *Aging Male*. 2003;6(2):86-93.
94. Raynaud JP, Legros JJ, Rollet J, et al. Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every 2 days for 1 year to hypogonadal men. *J Steroid Biochem Mol Biol* 2008;109:168.
95. Reid IR, Wattie DJ, Evans MC, et al. Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med* 1996;156:1173.
96. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. *Int J Impot Res* 2006;18(2):201-5.
97. Ross RJM, Siyambalapitiya S, Jonsson P, Koltowska-Haggstrom M, Gaillard R, Ho K. Cross-sectional analysis of testosterone therapies in hypopituitary men on stable pituitary hormone replacement. *Clin Endocrinol* 2009;70(6):907-13.
98. Saad F, Gooren LJ, Haider A, et al. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. *J Androl* 2008;29:102.
99. Saeedi M, Kosaryan M, Fekri K, et al. A randomized, double-blind, controlled trial of testosterone gel treatment versus vehicle control on the facial hair of young men with beta-thalassemia major. *J Dermatol Treat* 2007;18:271.
100. Schubert M, Bullmann C, Minnemann T, et al. Osteoporosis in male hypogonadism: responses to androgen substitution differ among men with primary and secondary hypogonadism. *Hormone Res* 2003;60:21.
101. Schubert M, Minnemann T, Hubler D, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab* 2004;89:5429.
102. Schwartz JB, Volterrani M, Caminiti G, et al. Effects of testosterone on the Q-T interval in older men and older women with chronic heart failure. *Int J Androl* 2011;34:e415.
103. Seftel AD, Mack RJ, Secrest AR, Smith TM. Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. *J Androl*. 2004;25(6):963-972.
104. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol*. 2004;172(2):658-663.

105. Sheffield-Moore M, Dillon EL, Caspersen SL, et al. A randomized pilot study of monthly cycled testosterone replacement or continuous testosterone replacement versus placebo in older men. *J Clin Endocrinol Metab.* 2011;96(11):E1831-E1837.
106. Shigehara K, Sugimoto K, Konaka H, et al. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomised controlled study. *Aging Male* 2011;14:53.
107. Shores MM, Kivlahan DR, Sadak TI, Li EJ, Matsumoto AM. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J Clin Psychiatry.* 2009;70(7):1009-16.
108. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab.* 2012;97(6):2050-2058.
109. Sih R, Morley JE, Kaiser FE, Perry HM, III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab.* 1997;82(6):1661-1667.
110. Simon D, Charles MA, Lahlou N, et al. Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care.* 2001;24(12):2149-2151.
111. Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med.* 2012;157(10):681-91.
112. Spitzer M, Basaria S, Travison TG, Davda MN, DeRogatis L, Bhasin S. The effect of testosterone on mood and well-being in men with erectile dysfunction in a randomized, placebo-controlled trial. *Andrology.* 2013;1(3):475-82.
113. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95:639.
114. Stanworth RD, Akhtar S, Channer KS, et al. The role of androgen receptor CAG repeat polymorphism and other factors which affect the clinical response to testosterone replacement in metabolic syndrome and type 2 diabetes: TIMES2 sub-study. *Eur J Endocrinol* 2014;170:193.
115. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab.* 2003;88(6):2673-81.
116. Stout M, Tew GA, Doll H, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *Am Heart J* 2012;164:893.
117. Strollo F, Strollo G, More M, et al. Low-intermediate dose testosterone replacement therapy by different pharmaceutical preparations improves frailty score in elderly hypogonadal hyperglycaemic patients. *Aging Male.* 2013;16(2):33-37.
118. Sullivan DH, Roberson PK, Johnson LE, et al. Effects of muscle strength training and testosterone in frail elderly males. *Med Sci Sports Exerc.* 2005;37(10):1664-1672.
119. Svartberg J, Agledahl I, Figenschau Y, et al. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20:378.
120. Swerdloff RS, Wang C, Cunningham G, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85(12):4500-10.
121. Swerdloff RS, Wang C. Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel. *Aging Male.* 2003;6(3):207-11.
122. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male.* 2003;6(1):13-7.
123. Tan WS, Low WY, Ng CJ, et al. Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. *BJU Int* 2013;111:1130.
124. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: Efficacy and treatment cost. *J Sex Med* 2010;7(Part 1):269-76.
125. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 1992;75(4):1092-8.
126. Thomson S, Koren G, Van SV, Rieder M, Van Uum SHM. Testosterone concentrations in hair of hypogonadal men with and without testosterone replacement therapy. *Therapeutic Drug Monitor* 2009;31(6):779-82.
127. Tong SF, Ng CJ, Lee BC, et al. Effect of long-acting testosterone undecanoate treatment on quality of life in men with testosterone deficiency syndrome: a double blind randomized controlled trial. *Asian J Androl* 2012;14:604.
128. Trabado S, Maione L, Bry-Gauillard H, et al. Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/kallmann syndrome and effects of different modalities of hormonal treatment: A single-center study of 281 patients. *J Clin Endocrinol Metab.* 2014;99(2):E268-E275.
129. Trabado S, Maione L, Salenave S, et al. Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities of hormonal treatment. *Fertil Steril* 2011;95(7):2324-9.
130. Travison TG, Basaria S, Storer TW, et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci.* 2011;66(10):1090-1099.

131. van den Bergh JP, Hermus AR, Spruyt AI, Sweep CG, Corstens FH, Smals AG. Bone mineral density and quantitative ultrasound parameters in patients with Klinefelter's syndrome after long-term testosterone substitution. *Osteoporos Int* 2001;12(1):55-62.
132. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. *J Androl* 2007;28(6):875-82.
133. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829-36.
134. Vignera S. La, Calogero AE, D'Agata R, et al. Testosterone therapy improves the clinical response to conventional treatment for male patients with metabolic syndrome associated to late onset hypogonadism. *Minerva Endocrinologica* 2008;33:159.
135. Vignera S. La, Condorelli R, Vicari E, et al. Original immunophenotype of blood endothelial progenitor cells and microparticles in patients with isolated arterial erectile dysfunction and late onset hypogonadism: Effects of androgen replacement therapy. *Aging Male* 2011;14(3):183-9.
136. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab.* 2004;89(5):2085-98.
137. Wang C, Swerdloff RS, Iranmanesh A, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clinical Endocrinology.* 2001;54(6):739-750.
138. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85(8):2839-2853.
139. Wang YJ, Zhan JK, Huang W, et al. Effects of low-dose testosterone undecanoate treatment on bone mineral density and bone turnover markers in elderly male osteoporosis with low serum testosterone. *Int J Endocrinol* 2013;570413.
140. Yaron M, Greenman Y, Rosenfeld JB, et al. Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. *Eur J Endocrinol.* 2009;160(5):839-846.
141. Zhang XW, Liu ZH, Hu XW, et al. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. *Chin Med J.* 2012;125(21):3806-3810.
142. Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E. Prostate volume and growth in testosterone-substituted hypogonadal men are dependent on the CAG repeat polymorphism of the androgen receptor gene: a longitudinal pharmacogenetic study. *J Clin Endocrinol Metab.* 2003;88(5):2049-54.

APPENDIX 3: LIST OF RECORDS EXCLUDED AT FULL-TEXT REVIEW

1. A long-acting depot formulation of testosterone (Aveed). *Med Lett Drugs Ther* 2014;56(1439):26-8
2. Acbay O., M.S. Gonen, P. Kadioglu, S. Gundogdu. The effects of testosterone replacement on serum lipids and body composition in young men with hypogonadism. *Klinik Gelisim* 1996;9(1):4013-8.
3. Adamopoulos D.A., S. Nicopoulou, N. Kapolla, M. Karamertzanis, E. Andreou. The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia. *Fertil Steril* 1997;67(4):756-62.
4. Adamopoulos D.A., S. Nicopoulou, N. Kapolla, P. Vassilopoulos, M. Karamertzanis, L. Kontogeorgos. Endocrine effects of testosterone undecanoate as a supplementary treatment to menopausal gonadotropins or tamoxifen citrate in idiopathic oligozoospermia. *Fertil Steril* 1995;64(4):818-24.
5. Ajayi A.A., R. Mathur, P.V. Halushka. Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. *Circulation*. 1995; 91(11):2742-7.
6. Akcam T., E. Bolu, A.L. Merati, C. Durmus, M. Gerek, Y. Ozkaptan. Voice changes after androgen therapy for hypogonadotrophic hypogonadism. *Laryngoscope* 2004;114(9):1587-91.
7. Al Mukaddam M., C.S. Rajapakse, Y.A. Bhagat, F.W. Wehrli, W. Guo, H. Peachey, S.O. LeBeau, B.S. Zemel, C. Wang, R.S. Swerdloff, S.C. Kapoor, P.J. Snyder. Effects of testosterone and growth hormone on the structural and mechanical properties of bone by micro-MRI in the distal tibia of men with hypopituitarism. *Journal of Clinical Endocrinology and Metabolism*. 2014;99(4):1236
8. Al-Futaisi A.M., I.S. Al-Zakwani, A.M. Almahrezi, D. Morris. Subcutaneous administration of testosterone. A pilot study report. *Saudi Med J* 2006;27(12):1843-6.
9. Aliaev I.G., A.Z. Vinarov, N.D. Akhvediani. Choice of treatment of erectile dysfunction associated with hypogonadism. *Urologiia* 2010;37.
10. Alkalay D., L. Khemani, W.E. Wagner, M.F. Bartlett. Sublingual and oral administration of methyltestosterone. A comparison of drug bioavailability. *J Clin Pharmacol New Drugs* 1973;13(4):142-51.
11. Allan C.A., B.J. Strauss, H.G. Burger, E.A. Forbes, R.I. McLachlan. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metabol* 2008;93(1):139-46.
12. Allan C.A., B.J. Strauss, H.G. Burger, E.A. Forbes, R.I. McLachlan. The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men. *Med J Aust* 2006;185(8):424-7.
13. Allan C.A., E.A. Forbes, B.J. Strauss, R.I. McLachlan. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. *Int J Impot Res* 2008;20(4):396-401.
14. Allen T.W. Testosterone replacement therapy in hypogonadal men. *J Am Osteopath Ass* 1993;93(5):552.
15. Aloisi A.M., I. Ceccarelli, M. Carlucci, A. Suman, G. Sindaco, S. Mameli, V. Paci, L. Ravaioli, G. Passavanti, V. Bachiocco, G. Pari. Hormone replacement therapy in morphine-induced hypogonadic male chronic pain patients. *Reprod Biol Endocrinol* 2011;9:26.
16. Aly F.W. Clinical experiences with a non-virilizing, oral-acting testosterone derivative (dehydro-17-methyltestosterone) (I). *Die Medizinische Welt* 1961;12:2468.
17. Amano T., T. Imao, K. Takemae, T. Iwamoto, K. Yamakawa, K. Baba, M. Nakanome, H. Sugimori, T. Tanaka, K. Yoshida, T. Katabami, M. Tanaka. Profile of serum testosterone levels after application of testosterone ointment (glowmin) and its clinical efficacy in late-onset hypogonadism patients. *J Sex Med* 2008;5(7):1727-36.
18. Amano T., T. Imao, K. Takemae, T. Iwamoto, M. Nakanome. Testosterone replacement therapy by testosterone ointment relieves lower urinary tract symptoms in late onset hypogonadism patients. *Aging Male* 2010;13(4):242-6.
19. Amiaz R., H.G. Pope, T. Mahne, J.F. Kelly, B.P. Brennan, G. Kanayama, M. Weiser, J.I. Hudson, S.N. Seidman. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: a randomized, placebo-controlled clinical trial. *J Sex Marital Ther* 2011;37(4):243-54.
20. Aminorroaya A., S. Kelleher, A.J. Conway, L.P. Ly, D.J. Handelsman. Adequacy of androgen replacement influences bone density response to testosterone in androgen-deficient men. *Eur J Endocrinol* 2005;152(6):881-6.
21. Amory J.K., H.A. Chansky, K.L. Chansky, M.R. Camuso, C.T. Hoey, B.D. Anawalt, A.M. Matsumoto, W.J. Bremner. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. *J Am Geriatr Soc* 2002;50(10):1698-701.
22. Amory J.K., M.A. Bush, H. Zhi, R.B. Caricofe, A.M. Matsumoto, R.S. Swerdloff, C. Wang, R.V. Clark. Oral testosterone with and without concomitant inhibition of 5 α -reductase by dutasteride in hypogonadal men for 28 days. *J Urol* 2011;185:626.
23. Amory J.K.. Study clarifies associations between hypogonadism and health in aging men. *Asian J Androl* 2012;14(6):809-10.
24. Anderson F.H., R.M. Francis, K. Faulkner. Androgen supplementation in eugonadal men with osteoporosis-effects of 6 months of treatment on bone mineral density and cardiovascular risk factors. *Bone* 1996;18(2):171-7.
25. Anderson R.A., C.A. Ludlam, F.C.W. Wu. Haemostatic effects of supraphysiological levels of testosterone in normal men. *Thromb Haemostasis* 1995;74(2):693-7.

26. Anderson R.A., C.W. Martin, A.W. Kung, D. Everington, T.C. Pun, K.C. Tan, J. Bancroft, K. Sundaram, A.J. Moo-Young, D.T. Baird. 7Alpha-methyl-19-nortestosterone maintains sexual behavior and mood in hypogonadal men. *J Clin Endocrinol Metab* 1999;84(10):3556-62.
27. Anderson R.A., F.C. Wu. Comparison between testosterone enanthate-induced azoospermia and oligozoospermia in a male contraceptive study. II. Pharmacokinetics and pharmacodynamics of once weekly administration of testosterone enanthate. *J Clin Endocrinol Metab* 1996;81(3):896-901.
28. Asscheman H., L.J. Gooren. Scrotal testosterone patches: a good addition to therapeutic options for hypogonadal men. *Nederlands Tijdschrift voor Geneeskunde*. 2000;144:847.
29. Aszpis S., S. Karlsbrum, H. Salerni, P. Otero, L. Schurman, O. Levalle. Different somatic and densitometric responses of cortical and trabecular bone to androgen therapy in hypogonadal men. *Revista Argentina de Endocrinologia y Metabolismo* 2007;44(4):223-31.
30. Aversa A., A.M. Isidori, G. Spera, A. Lenzi, A. Fabbri. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol* 2003;58(5):632-8.
31. Aydin S., O. Odabas, M. Ercan, H. Kara, M.Y. Agargun. Efficacy of testosterone, trazodone and hypnotic suggestion in the treatment of non-organic male sexual dysfunction. *Br J Urol* 1996;77(2):256-60.
32. Aydogan U., A. Aydogdu, H. Akbulut, A. Sonmez, S. Yuksel, Y. Basaran, O. Uzun, E. Bolu, K. Saglam. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. *Endocr J* 2012;59(12):1099-105.
33. Aydogan U., A. Eroglu, H. Akbulut, Y. Yildiz, D.E. Gok, A. Sonmez, T. Aydin, E. Bolu, K. Saglam. Evaluation of the isokinetic muscle strength, balance and anaerobic performance in patients with young male hypogonadism. *Endocr J* 2012;59(4):321-7.
34. Ayesh R., S.C. Mitchell, R.L. Smith. Dysfunctional N-oxidation of trimethylamine and the influence of testosterone treatment in man. *Pharmacogenetics* 1995;5(4):244-6.
35. Bachman, R. Feng, T. Travison, M. Li, G. Olbina, V. Ostland, J. Ulloor, A. Zhang, S. Basaria, T. Ganz, M. Westerman, S. Bhasin. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. *J Clin Endocrinol Metabolism* 2010;95(10):4743-7.
36. Bagatell C.J., J.R. Heiman, A.M. Matsumoto, J.E. Rivier, W.J. Bremner. Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. *J Clin Endocrinol Metab* 1994;79(2): 561-7.
37. Baisley K.J., M.J. Boyce, S. Bukofzer, R. Pradhan, S.J. Warrington. Pharmacokinetics, safety and tolerability of three dosage regimens of buccal adhesive testosterone tablets in healthy men suppressed with leuporelin. *J Endocrinol* 2002;175(3):813-9.
38. Bakhshi V., M. Elliott, A. Gentili, M. Godschalk, T. Mulligan. Testosterone improves rehabilitation outcomes in ill older men. *J Am Geriatr Soc* 2000;48(5):550-3.
39. Ball J.H., E.G. Lowrie, C.L. Hampers, J.P. Merrill. Testosterone therapy in hemodialysis patients. *Clin Nephrol*. 1975;4(3):91-8.
40. Bals-Pratsch M., U.A. Knuth, Y.D. Yoon, E. Nieschlag. Transdermal testosterone substitution therapy for male hypogonadism. *Lancet* 1986;2(8513):943-6.
41. Banerjee C., J. Ulloor, E.L. Dillon, Q. Dahodwala, B. Franklin, T. Storer, P. Sebastiani, M. Sheffield-Moore, R.J. Urban, S. Bhasin, M. Montano. Identification of serum biomarkers for aging and anabolic response. *Immun Ageing* 2011;8(1):5.
42. Basu R., M.C. Dalla, M. Campioni, A. Basu, K.S. Nair, M.D. Jensen, S. Khosla, G. Klee, G. Toffolo, C. Cobelli, R.A. Rizza. Effect of 2 years of testosterone replacement on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, and postprandial glucose turnover in elderly men. *Diabetes Care* 2007;30(8):1972-8.
43. Bauman W.A., C.M. Ciriigliaro, M.F. La Fountaine, A.M. Jensen, J.M. Wecht, S.C. Kirshblum, A.M. Spungen. A small-scale clinical trial to determine the safety and efficacy of testosterone replacement therapy in hypogonadal men with spinal cord injury. *Horm Metab Res* 2011;43:574-9.
44. Baysan O., E. Bolu, S. Demirkol, K. Erinc, A. Hasimi, F. Deniz, M. Yokusoglu, M. Uzun, F. Kilicarslan, E. Isik. The effect of testosterone therapy on QT dispersion in patients with secondary hypogonadism. *Gulhane Medical Journal* 48(1):22-4.
45. Becker U., C. Gluud, P. Bennett. The effect of oral testosterone on serum TBG levels in alcoholic cirrhotic men. *Liver*. 1988;8(4):219-24.
46. Bedrossian R.H., D.S. Pocock, Jr Harvey, A.S. Sindoni. Diabetic retinopathy treated with testosterone. *Arch Ophthalmol* 1953;50(3):277-81.
47. Bedrossian R.H., D.S. Pocock, Jr Harvey, A.S. Sindoni. Diabetic retinopathy treated with testosterone. *Arch Ophthalmol* 1951;50(3):177-81.
48. Behre H.M., E. Nieschlag. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. *J Clin Endocrinol Metab* 1992;75(5):1204-10.
49. Behre H.M., Eckardstein S. von, S. Kliesch, E. Nieschlag. Long-term substitution therapy of hypogonadal men with transscrotal testosterone over 7-10 years. *Clin Endocrinol* 1999;50(5):629-35.
50. Behre H.M., J. Bohmeyer, E. Nieschlag. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol* 1994;40(3):341-9.

51. Behre H.M., L. Heinemann, A. Morales, C. Pexman-Fieth. Rationale, design and methods of the ESPRIT study: Energy, Sexual desire and body Proportions with AndroGel, Testosterone 1% gel therapy, in hypogonadal men. *Aging Male* 2008;11(2):101-6.
52. Benito M., B. Vasilic, F.W. Wehrli, B. Bunker, M. Wald, B. Gomberg, A.C. Wright, B. Zemel, A. Cucchiara, P.J. Snyder. Effect of testosterone replacement on trabecular architecture in hypogonadal men. *J Bone Miner Res* 2005;20(10):1785-91.
53. Benkert O., W. Witt, W. Adam, A. Leitz. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. *Arch Sex Behav* 1979;8(6):471-9.
54. Bernini G., D. Versari, A. Moretti, A. Virdis, L. Ghiadoni, M. Bardini, C. Taurino, D. Canale, S. Taddei, A. Salvetti. Vascular reactivity in congenital hypogonadal men before and after testosterone replacement therapy. *J Clin Endocrinol Metab* 2006;91(5):1691-7.
55. Bertelloni S., G.I. Baroncelli, M. Ferdeghini, G. Perri, G. Saggese. Normal volumetric bone mineral density and bone turnover in young men with histories of constitutional delay of puberty. *J Clin Endocrinol Metab* 1998;83(12):4280-3.
56. Bhasin S., R.A. Parker, F. Sattler, R. Haubrich, B. Alston, T. Umbleja, C.M. Shikuma, AIDS Clinical Trials Group. Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. *J Clin Endocrinol Metab* 2007;92(3):1049-57.
57. Bhasin S., T.G. Travison, T.W. Storer, K. Lakshman, M. Kaushik, N.A. Mazer, A.H. Ngyuen, M.N. Davda, H. Jara, A. Aakil, S. Anderson, P.E. Knapp, S. Hanka, N. Mohammed, P. Daou, R. Miciek, J. Ulloor, A. Zhang, B. Brooks, K. Orwoll, L. Hede-Brierley, R. Eder, A. Elmi, G. Bhasin, L. Collins, R. Singh, S. Basaria. Effect of testosterone supplementation with and without a dual 5alpha-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA* 2012;307(9):931-9.
58. Bhasin S., T.W. Storer, N. Berman, C. Callegari, B. Clevenger, J. Phillips, T.J. Bunnell, R. Tricker, A. Shirazi, R. Casaburi. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *NEJM* 1996; 335(1):1-7.
59. Bhasin S., R.S. Swerdloff, B. Steiner, M.A. Peterson, T. Meridores, M. Galmirini, M.R. Pandian, R. Goldberg, N. Berman. A biodegradable testosterone microcapsule formulation provides uniform eugonadal levels of testosterone for 10-11 weeks in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism*. 1992/01//. 74:75
60. Bhattacharya R.K., M. Khera, G. Blick, H. Kushner, D. Nguyen, M.M. Miner. Effect of 12 months of testosterone replacement therapy on metabolic syndrome components in hypogonadal men: data from the Testim Registry in the US (TRiUS). *BMC Endocr Disord*. 2011//. 11:18, 2011. #pages#
61. Bhattacharya R.K., M. Khera, G. Blick, H. Kushner, M.M. Miner. Testosterone replacement therapy among elderly males: the Testim Registry in the US (TRiUS). *Clin Interv Aging* 2012;7:321-30.
62. Birzniece V., U.J. Meinhardt, D.J. Handelsman, K.K.Y. Ho. Testosterone stimulates extra-hepatic but not hepatic fat oxidation (Fox): Comparison of oral and transdermal testosterone administration in hypopituitary men. *Clin Endocrinol* 2009;71(5):715-21.
63. Birzniece V., U.J. Meinhardt, M.A. Umpleby, D.J. Handelsman, K.K. Ho. Interaction between testosterone and growth hormone on whole-body protein anabolism occurs in the liver. *J Clin Endocrinol Metab* 2011;96(4):1060-7.
64. Bizzarro A., G. Valentini, Martino G. Di, A. DaPonte, Bellis A. De, G. Iacono. Influence of testosterone therapy on clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome. *J Clin Endocrinol Metab* 1987;64(1):32-6.
65. Blackman M.R., J.D. Sorkin, T. Munzer, M.F. Bellantoni, J. Busby-Whitehead, T.E. Stevens, J. Jayme, K.G. O'Connor, C. Christmas, J.D. Tobin, K.J. Stewart, E. Cottrell, Clair C. St, K.M. Pabst, S.M. Harman. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 2002;288(18):2282-92.
66. Blazeovich A.J., A. Giorgi. Effect of testosterone administration and weight training on muscle architecture. *Med Sci Sports Exerc* 2001;33(10):1688-93.
67. Blick G., M. Khera, R.K. Bhattacharya, D. Nguyen, H. Kushner, M.M. Miner. Testosterone replacement therapy outcomes among opioid users: the Testim Registry in the United States (TRiUS). *Pain Med* 2012;13(5):688-98.
68. Blick G., M. Khera, R.K. Bhattacharya, H. Kushner, M.M. Miner. Testosterone replacement therapy in men with hypogonadism and HIV/AIDS: results from the TRiUS registry. *Postgrad Med* 2013;125(2):19-29.
69. Bojesen, K. Kristensen, N.H. Birkebaek, J. Fedder, L. Mosekilde, P. Bennett, P. Laurberg, J. Frystyk, A. Flyvbjerg, J.S. Christiansen, C.H. Gravholt. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care* 2006;29(7):1591-8.
70. Bolu E., A. Sonmez, S. Tapan, A. Taslipinar, A. Aydogdu, C. Meric, Y. Basaran, G. Uckaya, M. Serdar, I. Kurt, O. Azal. HDL cholesterol subfractions and the effect of testosterone replacement in hypogonadism. 2013;45(6):443-8.
71. Bondanelli M., M.R. Ambrosio, A. Margutti, P. Franceschetti, M.C. Zatelli, E.C. Degli Uberti. Activation of the somatotrophic axis by testosterone in adult men: Evidence for a role of hypothalamic growth hormone-releasing hormone. *Neuroendocrinology* 2003;77(6):380-87.
72. Bouloux P.M., J.J. Legros, J.M. Elbers, T.B. Geurts, M.J. Kaspers, A.G. Meehan, E.J. Meuleman, Study 43203 Investigators. Effects of oral testosterone undecanoate therapy on bone mineral density and body composition in

- 322 aging men with symptomatic testosterone deficiency: a 1-year, randomized, placebo-controlled, dose-ranging study. *Aging Male* 2013;16(2):38-47.
73. Braatvedt G.D.. Outcome of managing impotence in clinical practice. *N Z Med J* 1999;112:272-4.
74. Brabrand S., S.D. Fossa, M. Cvancarova, G. Lehne. Androgen substitution with testosterone undecanoate in survivors of bilateral testicular cancer requires individually-adjusted injection intervals. *BJU Int* 2011;107(7):1080-7.
75. Bramswig J.H., E. Nieschlag, G. Schellong. Pituitary-gonadal function in boys after high dose testosterone treatment for excessively tall stature. *Acta Endocrinol* 1984;107(1):97-103.
76. Brauck K., C.J. Galban, S. Maderwald, B.L. Herrmann, M.E. Ladd. Changes in calf muscle elasticity in hypogonadal males before and after testosterone substitution as monitored by magnetic resonance elastography. *Eur J Endocrinol* 2007;156(6):673-8.
77. Brill K.T., A.L. Weltman, A. Gentili, J.T. Patrie, D.A. Fryburg, J.B. Hanks, R.J. Urban, J.D. Veldhuis. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. *J ClinEndocrinol Metab* 2002;87(12):5649-57.
78. Brisson G.R., Sainz A. Gutierrez, C. Ayotte, R. Gareau, L. Senecal, M.J. Castillo. Influence of a transscrotal testosterone propionate administration on the serum level of selected hormones of the hypophyso-gonadal axis. *J Steroid Biochem Mol Biol* 1997;62(1):65-71.
79. Brocks D.R., A.W. Meikle, S.C. Boike, N.A. Mazer, N. Zariffa, P.R. Audet, D.K. Jorkasky. Pharmacokinetics of testosterone in hypogonadal men after transdermal delivery: influence of dose. *J Clin Pharmacol* 1996;36(8):732-9.
80. Buisson J. Effects of testosterone supplementation on sexual function in elderly men: Results of a six month randomised, placebo controlled study. *Cahiers de l'Annee Gerontologique* 2010;2(3):144-6.
81. Buisson J. Oral testosterone substitution therapy in age-associated hypogonadism: Benefits and safety (information from a randomised trial against placebo). *Cahiers de l'Annee Gerontologique* 2010;2(3):148-51.
82. Burger H.G., H.W. Baker. Therapeutic considerations and results of gonadotropin treatment in male hypogonadotropic hypogonadism. *Ann N Y Acad Sci* 1984;438:447-53.
83. Burris A.S., R.H. Gracely, C.S. Carter, R.J. Sherins, J.M. Davidson. Testosterone therapy is associated with reduced tactile sensitivity in human males. *Horm Behav* 1991;25(2):195-205.
84. Burris A.S., S.M. Banks, C.S. Carter, J.M. Davidson, R.J. Sherins. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl* 1992;13(4):297-304.
85. Buvat J., F. Montorsi, M. Maggi, H. Porst, A. Kaipia, M.H. Colson, B. Cuzin, I. Moncada, A. Martin-Morales, A. Yassin, E. Meuleman, I. Eardley, J.D. Dean, R. Shabsigh. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 2011;8(1):284-93.
86. Cai Y.B., W.D. Zhong, G.Q. Zeng, J.B. Hu, H.A. Wei. [A clinical study on the efficacy of androgen replacement in the treatment of elderly patients with androgen-deficiency]. *Chinese Journal of Geriatrics* 2001;20:453.
87. Cakir E., O. Ozcan, H. Yaman, E.O. Akgul, C. Bilgi, M.K. Erbil, Z. Yesilova. Elevated plasma concentration of asymmetric dimethylarginine that is reduced by single dose testosterone administration in idiopathic hypogonadotropic hypogonadism patients. *J Clin Endocrinol Metab* 2005; 90(3):1651-4.
88. Campfield L.A., C. Saul, R.Z. Sokol. The effect of chronic administration of testosterone enanthate on the glucose tolerance of normal men. *Clin Res* 1980;28(1):47A.
89. Canguven O., G. Aykose, S. Albayrak, C. Goktas, R. Horuz, F. Yencilek. Efficacy of testosterone gel in the treatment of erectile dysfunction in hypogonadal hemodialysis patients: a pilot study. *Int J Impot Res* 2010;22(2):140-5.
90. Carani C., A. Scuteri, P. Marrama, J. Bancroft. The effects of testosterone administration and visual erotic stimuli on nocturnal penile tumescence in normal men. *Horm Behav* 1990;24(3):435-41.
91. Carani C., D. Zini, A. Baldini, Casa L. Della, A. Ghizzani, P. Marrama. Effects of androgen treatment in impotent men with normal and low levels of free testosterone. *Arch Sex Behav* 1990;19(3):223-34.
92. Carani C., M.F. Celani, D. Zini, A. Baldini, Casa L. Della, P. Marrama. Changes in the bioactivity to immunoreactivity ratio of circulating luteinizing hormone in impotent men treated with testosterone undecanoate. *Acta Endocrinol* 1989;120(3):284-8.
93. Casaburi R., G. Cosentino, S. Bhasin, M. Fournier, M. Lewis, J. Porszasz, T. Storer. A randomised trial of strength training and testosterone supplementation in men with chronic obstructive pulmonary disease. *Eur Respir J* 2001;18:173s.
94. Casaburi R., S. Bhasin, L. Cosentino, J. Porszasz, A. Somfay, M.I. Lewis, M. Fournier, T.W. Storer. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170(8):870-8.
95. Casaburi R., L. Cosentino, J. Porszasz, S. Bhasin, T. Storer. Hormonal and safety profile resulting from physiologic testosterone supplementation in men with COPD. *Am J Respir Critical Care Med* 2002;165:A506.
96. Cavender R.K., M. Fairall. Subcutaneous testosterone pellet implant (Testopel) therapy for men with testosterone deficiency syndrome: a single-site retrospective safety analysis. *J Sex Med* 2009;6(11):3177-92.

97. Chapman I.M., R. Visvanathan, A.J. Hammond, J.E. Morley, J.B. Field, K. Tai, D.P. Belobrajdic, R.Y. Chen, M. Horowitz. Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. *Am J Clin Nutr* 2009;89(3):880-9.
98. Chatterjee R., P.D. Kottaridis, H.H. McGarrigle, D.C. Linch. Management of erectile dysfunction by combination therapy with testosterone and sildenafil in recipients of high-dose therapy for haematological malignancies. *Bone Marrow Transplant* 2002;29(7):607-10.
99. Chatterjee R., S. Wood, H.H. McGarrigle, W.R. Lees, D.J. Ralph, G.H. Neild. A novel therapy with testosterone and sildenafil for erectile dysfunction in patients on renal dialysis or after renal transplantation. *J Fam Plann Reprod Health Care* 2004;30(2):88-90.
100. Chavoshan B., M. Fournier, M.I. Lewis, T.W. Storer, X. Da, R. Casaburi. Effects of resistance training and testosterone replacement on skeletal muscle eNOS and iNOS protein levels in men with COPD [Abstract]. *Proc Am Thorac Soc* 2006;A320.
101. Chavoshan, M. Fournier, M.I. Lewis, J. Porszasz, T.W. Storer, X. Da, M. Rambod, R. Casaburi. Testosterone and resistance training effects on muscle nitric oxide synthase isoforms in COPD men. *Respir Med* 2012;106(2):269-75.
102. Chen F., R. Lam, D. Shaywitz, R.C. Hendrickson, G.J. Opitck, D. Wishengrad, A. Liaw, Q. Song, A.J. Stewart, C.E. Cummings, C. Beals, K.E. Yarasheski, A. Reicin, M. Ruddy, X. Hu, N.A. Yates, J. Menetski, G.A. Herman. Evaluation of early biomarkers of muscle anabolic response to testosterone. *J Cachexia Sarcopenia Muscle* 2011;2(1):45-56.
103. Cherrier M., S. Asthana, Set al Plymate. Testosterone treatment in Alzheimer's disease and healthy older men. Proceedings of the 6th International Conference on Alzheimer's Disease and Related Disorders; 1998;19:S302.
104. Cherrier M.M., A.M. Matsumoto, J.K. Amory, S. Ahmed, W. Bremner, E.R. Peskind, M.A. Raskind, M. Johnson, S. Craft. The role of aromatization in testosterone supplementation: effects on cognition in older men. *Neurology* 2005;64(2):290-6.
105. Cherrier M.M., A.M. Matsumoto, J.K. Amory, S. Asthana, W. Bremner, E.R. Peskind, M.A. Raskind, S. Craft. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005;64(12):2063-8.
106. Cherrier M.M., B.D. Anawalt, K.L. Herbst, J.K. Amory, S. Craft, A.M. Matsumoto, W.J. Bremner. Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. *J Clin Endocrinol Metab* 2002;87(7):3090-6.
107. Cherrier M.M., S. Asthana, S. Plymate, L. Baker, A.M. Matsumoto, E. Peskind, M.A. Raskind, K. Brodtkin, W. Bremner, A. Petrova, S. Latendresse, S. Craft. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology* 2001;57(1):80-8.
108. Cherrier M.M., S. Craft, A.H. Matsumoto. Cognitive Changes Associated with Supplementation of Testosterone or Dihydrotestosterone in Mildly Hypogonadal Men: A Preliminary Report. *J Androl* 2003;24(4):568-76.
109. Cherrier M.M., S. Plymate, S. Mohan, S. Asthana, A.M. Matsumoto, W. Bremner, E. Peskind, M. Raskind, S. Latendresse, A.P. Haley, S. Craft. Relationship between testosterone supplementation and insulin-like growth factor-I levels and cognition in healthy older men. *Psychoneuroendocrinology* 2004;29(1):65-82.
110. Chiang P.H., F.M. Fang, W.C. Jong, T.J. Yu, Y.C. Chuang, H.J. Wang. High-dose rate iridium-192 brachytherapy and external beam radiation therapy for prostate cancer with or without androgen ablation. *Int J Urol* 2004;11(3):152-8.
111. Chik Z., A. Johnston, A.T. Tucker, K. Kirby, C.A. Alam. Correcting endogenous concentrations of testosterone influences bioequivalence and shows the superiority of TDS(R)-testosterone versus Androgel(R). *Int J Clin Pharmacol Ther* 2009;47(4):262-8.
112. Chik Z., A. Johnston, A.T. Tucker, S.L. Chew, L. Michaels, C.A. Alam. Pharmacokinetics of a new testosterone transdermal delivery system, TDS-testosterone in healthy males. *Br J Clin Pharmacol* 2006;61(3):275-9.
113. Chlebowski R.T., J. Herrold, I. Ali, E. Oktay, J.S. Chlebowski, A.T. Ponce, D. Heber, J.B. Block. Influence of nandrolone decanoate on weight loss in advanced non-small cell lung cancer. *Cancer*. 1986;58(1):183-6.
114. Clark M.J., G.F. Petroski, M.O. Mazurek, K.J. Hagglund, A.K. Sherman, A.B. Lammy, M.K. Childers, M.E. Acuff. Testosterone replacement therapy and motor function in men with spinal cord injury: a retrospective analysis. *Am J Phys Med Rehabil* 2008;87(4):281-4.
115. Clay P.G. Program savings associated with switching testosterone intramuscular injections to topical gel in HIV infected males. *Cur Med Res Opin* 2004;20(4):461-8.
116. Clinical trial for testosterone gel. *J Phar Technol* 1997;13(3):137.
117. Clopper R.R., M.L. Voorhess, M.H. MacGillivray, P.A. Lee, B. Mills. Psychosexual behavior in hypopituitary men: a controlled comparison of gonadotropin and testosterone replacement. *Psychoneuroendocrinology* 1993;18(2):149-61.
118. Coevorden A. van, J.C. Stolear, M. Dhaene, J.L. van Herweghem, J. Mockel. Effect of chronic oral testosterone undecanoate administration on the pituitary-testicular axes of hemodialyzed male patients. *Clini Nephrol* 1986;26(1):48-54.
119. Colao A., Somma C. Di, S. Spiezia, M. Filippella, R. Pivonello, G. Lombardi. Effect of growth hormone (GH) and/or testosterone replacement on the prostate in GH-deficient adult patients. *J Clin Endocrinol Metab* 2003;88(1):88-94.

120. Comhaire F., F. Schoonjans, R. Abdelmassih, S. Gordts, R. Campo, M. Dhont, S. Milingos, J. Gerris. Does treatment with testosterone undecanoate improve the in-vitro fertilizing capacity of spermatozoa in patients with idiopathic testicular failure? (Results of a double blind study). *Hum Reprod* 1995;10(10):2600-2.
121. Comhaire F.. Treatment of idiopathic testicular failure with high-dose testosterone undecanoate: a double-blind pilot study. *Fertil Steril* 1990;54:689-93.
122. Conaglen H.M., R.G. Paul, T. Yarnley, J. Kamp, M.S. Elston, J.V. Conaglen. Retrospective investigation of testosterone undecanoate depot for the long-term treatment of male hypogonadism in clinical practice. *J Sex Med* 2014;11(2):574-82.
123. Conaglen J.V., H.M. Conaglen. The effects of treating male hypogonadism on couples' sexual desire and function. *J Sex Med*. 2009;6(2):456-63.
124. Connors W., K. Flinn, A. Morgentaler. Outcomes with the "V" implantation technique vs. standard technique for testosterone pellet therapy. *J Sex Med* 2011;8(12):3465-70.
125. Conway A.J., L.M. Boylan, C. Howe, G. Ross, D.J. Handelsman. Randomized clinical trial of testosterone replacement therapy in hypogonadal men. *Int J Androl* 1988;11(4):247-64.
126. Coodley G.O., M.K. Coodley. A trial of testosterone therapy for HIV-associated weight loss. *AIDS*. 1997;11(11):1347-52.
127. Cooper A.J., C.G. Smith, A.A. Ismail, J.A. Loraine. A controlled trial of Potensan Forte ("aphrodisiac" and testosterone combined) in impotence. *Ir J Med Sci* 1973;142(4):155-61.
128. Cooper C.S., P.J. Perry, A.E. Sparks, J.H. MacIndoe, W.R. Yates, R.D. Williams. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol* 1998;159(2):441-3.
129. Corcoran C., S. Grinspoon. The use of testosterone in the AIDS wasting syndrome. *Aids Clin Care*. 1999;11(4):25-6.
130. Cordes U., J. Happ. The importance of testosterone, estradiol and SHbG for the development of normal bone mass in eugonadal and hypogonadal men. *Osteologie* 1999;8(3):160-8.
131. Cornoldi, G. Caminiti, G. Marazzi, C. Vitale, R. Patrizi, M. Volterrani, M. Miceli, M. Fini, G. Spera, G. Rosano. Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease. *Int J Cardiol* 2010;142(1):50-5.
132. Corona G., E. Mannucci, L. Petrone, C. Schulman, G. Balercia, A.D. Fisher, V. Chiarini, G. Forti, M. Maggi. A comparison of NCEP-ATPIII and IDF metabolic syndrome definitions with relation to metabolic syndrome-associated sexual dysfunction. *J Sex Med* 2007;4(3):789-96.
133. Corona G., E. Mannucci, L. Petrone, G. Balercia, F. Paggi, A.D. Fisher, F. Lotti, V. Chiarini, D. Fedele, G. Forti, M. Maggi. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. *J Sex Med* 2007;4 (4 pt 4):1038-45.
134. Corona G., G. Rastrelli, G. Balercia, F. Lotti, A. Sforza, M. Monami, G. Forti, E. Mannucci, M. Maggi. Hormonal association and sexual dysfunction in patients with impaired fasting glucose: a cross-sectional and longitudinal study. *J Sex Med* 2012;9(6):1669-80.
135. Corrales J.J., M. Almeida, R. Burgo, M.T. Mories, J.M. Miralles, A. Orfao. Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men and partial androgen deficiency. *J Endocrinol* 2006;189(3):595-604.
136. Coward R.M., J. Simhan, C.C. Carson III. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. *BJU Int* 2009;103(9):1179-83.
137. Coward R.M., J. Simhan, C.C. Carson. Racial differences in hypogonadal improvement and prostate-specific antigen levels in hypogonadal men treated with testosterone replacement therapy. *Int Braz J Urol* 2010;36(6):700-7.
138. Crawford B.A., P.Y. Liu, M.T. Kean, J.F. Bleasel, D.J. Handelsman. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab* 2003;88(7):3167-76.
139. Crowne E.C., W.H. Wallace, C. Moore, R. Mitchell, W.H. Robertson, J.M. Holly, S.M. Shalet. Effect of low dose oxandrolone and testosterone treatment on the pituitary-testicular and GH axes in boys with constitutional delay of growth and puberty. *Clin Endocrinol* 1997;46(2):209-16.
140. Cruse L.M., J. Valeriano, F.B. Vasey, J.D. Carter. Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men. *J Clin Rheumatol* 2006;12(5):221-5.
141. Cutter C.B. Compounded percutaneous testosterone gel: use and effects in hypogonadal men. *J Am Board Fam Pract* 2001;14(1):22-32.
142. Daly R.C., T.P. Su, P.J. Schmidt, D. Pickar, D.L. Murphy, D.R. Rubinow. Cerebrospinal fluid and behavioral changes after methyltestosterone administration: preliminary findings. *Arch Gen Psychiatry* 2001;58(2):172-7.
143. Danek A., T.N. Witt, K. Mann, H.U. Schweikert, G. Romalo, A.R. La Spada, K.H. Fischbeck. Decrease in androgen binding and effect of androgen treatment in a case of X-linked bulbospinal neuronopathy. *Clin Investig* 1994;72(11):892-7.
144. Daniell H.W., R. Lentz, N.A. Mazer. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. *J Pain* 2006;7(3):200-10.

145. Davidson J.M., C.A. Camargo, E.R. Smith. Effects of androgen on sexual behavior in hypogonadal men. *J Clin Endocrinol Metab* 1979;48(6):955-8.
146. Davies B.J., T.J. Walsh, P.L. Ross, S.J. Knight, N. Sadetsky, P.R. Carroll, C.J. Kane. Effect of BMI on primary treatment of prostate cancer. *Urology* 2008;72(2):406-11.
147. De Feo M.L., M. Maggi, V. Guardabasso, D. Rodbard, G. Delitala, V. Fazzi, A.D. Genazzani, F. Facchinetti, G. Forti. Naloxone administration does not affect gonadotropin secretion in agonadal men either basally or during testosterone treatment. *J Clin Endocrinol Metab* 1986;63(1):257-61.
148. Dean J.D., C. Carnegie, J. Rodzvilla, T. Smith. Long-term effects of testim(r) 1% testosterone gel in hypogonadal men. *Rev Urol* 2004;6 Suppl 6:S22-9.
149. Deb P., S.K. Gupta, M.M. Godbole. Effects of short-term testosterone replacement on areal bone mineral density and bone turnover in young hypogonadal males. *Indian J Endocrinol Metab* 2012;16(6):947-51.
150. Dedov I.I., D.G. Kurbatov, R.V. Rozhivanov, A.E. Lepetukhin, S.A. Dubskii, N.P. Goncharov. Nebido in the treatment of hypogonadism syndrome and its complications in men. *Urologiia* 2011;11.
151. Demchenko A.N., L.I. Serdechnaia. Effect of exogenous testosterone on the excretion of luteinizing and follicle-stimulating hormones in hypogonadism. *Probl Endokrinol (Mosk)* 1980;26:32.
152. Devogelaer J.P., Cooman S. De, Deuxchaisnes C. Nagant de. Low bone mass in hypogonadal males. Effect of testosterone substitution therapy, a densitometric study. *Maturitas* 1992;15(1):17-23.
153. Di L.L., P. Sgro, F. Romanelli, M. Mazzarino, F. Donati, M.C. Bragano, S. Bianchini, V. Fierro, M. Casasco, F. Botre, A. Lenzi. Urinary and serum hormones profiles after testosterone enanthate administration in male hypogonadism: concerns on the detection of doping with testosterone in treated hypogonadal athletes. *J Endocrinol Invest* 2009;32(5):445-53.
154. Dimick D.F., M. Heron, E.E. Baulieu, M.F. Jayle. A comparative study of the metabolic fate of testosterone, 17 alpha-methyl-testosterone. 19-nor-testosterone. 17 alpha-methyl-19-nor-testosterone and 17 alpha-methylestr-5(10)-ene-17 beta-ol-3-one in normal males. *Clinica Chimica Acta* 1961;6:63-71.
155. Dinsmore W.W., M.G. Wyllie. The long-term efficacy and safety of a testosterone mucoadhesive buccal tablet in testosterone-deficient men. *BJU Int* 2012;110(2):162-9.
156. Dobs A.S., A.M. Matsumoto, C. Wang, M.S. Kipnes. Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. *Curr Med Res Opinion* 2004;20(5):729-38.
157. Dobs A.S., D.R. Hoover, M.C. Chen, R. Allen. Pharmacokinetic characteristics, efficacy, and safety of buccal testosterone in hypogonadal males: a pilot study. *J Clin Endocrinol Metab* 1998;83:33-9.
158. Dobs A.S., J. Cofrancesco, W.E. Nolten, A. Danoff, R. Anderson, C.D. Hamilton, J. Feinberg, D. Seekins, B. Yangco, F. Rhame. The use of a transscrotal testosterone delivery system in the treatment of patients with weight loss related to human immunodeficiency virus infection. *Am J Med* 1999;107(2):126-32.
159. Dobs A.S., P.S. Bachorik, S. Arver, A.W. Meikle, S.W. Sanders, K.E. Caramelli, N.A. Mazer. Interrelationships among lipoprotein levels, sex hormones, anthropometric parameters, and age in hypogonadal men treated for 1 year with a permeation-enhanced testosterone transdermal system. *J Clin Endocrinol Metab* 2001;86(3):1026-33.
160. Dobs, P. Norwood, S. Potts, E. Gould, S. Chitra. Testosterone 2% gel can normalize testosterone concentrations in men with low testosterone regardless of body mass index. *J Sex Med* 2014;11 (3):857-64.
161. Dohn K., V. Hvidt, J. Nielsen, L. Palm. Testosterone therapy in obliterating arterial lesions in the lower limbs. *Angiology* 1968;19(6):342-50.
162. Dresch C. Evolution of 352 adult patients treated with androgens: short and long-term results of a prospective study. *Haematol Blood Transfus* 1979;24:139-54.
163. Dupuy O., M. Palou, H. Mayaudon, D. Sarret, L. Bordier, J.M. Garcin, B. Bauduceau. De La Chapelle syndrome. *Presse M* 2001;30:369.
164. Eckardstein S. von, E. Nieschlag. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. *J Androl* 2002; 23(3):419-25.
165. Elizabeth J., R. Sharma, K.M.P. Kumar. The effect of testosterone replacement on waist hip ratio, serum leptin and lipid profile in hypogonadal subjects. *Biomed* 2008;28(2):96-9.
166. El-Sakka A.I., H.M. Hassoba, A.M. Elbakry, H.A. Hassan. Prostatic specific antigen in patients with hypogonadism: effect of testosterone replacement. *J Sex Med* 2005;2(2):235-40.
167. Emmelot-Vonk M.H., H.J. Verhaar, H.R. Nakhai-Pour, D.E. Grobbee, Y.T. van der Schouw. Low testosterone concentrations and the symptoms of testosterone deficiency according to the Androgen Deficiency in Ageing Males (ADAM) and Ageing Males' Symptoms rating scale (AMS) questionnaires. *Clin Endocrinol* 2011;74(4):488-94.
168. English K.M., N.E. Scutt, T.H. Jones, K.S. Channer. Low dose transdermal testosterone therapy in men with chronic stable angina does not affect leptin levels or body mass index [abstract]. *Clin Sci* 2000;99:20P.
169. English K.M., R.P. Steeds, T.H. Jones, M.J. Diver, K.S. Channer. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102(16):1906-11.
170. Essers U.. Effects of testosterone and methenolone on erythropoietin activity and erythropoiesis in patients with kidney failure. *Medizinische Welt* 1971;48:1918.

171. F. Saad, A. Haider, G. Doros, A. Traish. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity* (Silver Spring) 2013;21(10):1975-81.
172. Fabbro E. Del, J.M. Garcia, R. Dev, D. Hui, J. Williams, D. Engineer, J.L. Palmer, L. Schover, E. Bruera. Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial. *Support Care Cancer*. 2013;21(9):2599-607.
173. Fairfield W.P., J.S. Finkelstein, A. Klibanski, S.K. Grinspoon. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. *J Clin Endocrinol Metab* 2001;86(5):2020-6.
174. Fairfield W.P., M. Treat, D.I. Rosenthal, W. Frontera, T. Stanley, C. Corcoran, M. Costello, K. Parlman, D. Schoenfeld, A. Klibanski, S. Grinspoon. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. *J Appl Physiol* 2001;90(6):2166-71.
175. Farina E.L., S.D. Smithson, K.M. Fowler, B.A. Dworetzky, E.B. Bromfield, D.L. Schomer, F.W. Drislane, A.G. Herzog. A comparison of anastrozole plus testosterone versus placebo plus testosterone treatment of sexual dysfunction in men with epilepsy and hypogonadism. *Epilepsia*. 2008;49(Suppl 7):38.
176. Feneley M.R., M. Carruthers. Is testosterone treatment good for the prostate? Study of safety during long-term treatment. *J Sex Med* 2012;9(8):2138-49.
177. Ferlin A., M. Schipilliti, C. Vinanzi, A. Garolla, Di A. Mambro, R. Selice, A. Lenzi, C. Foresta. Bone mass in subjects with klinefelter syndrome: Role of testosterone levels and androgen receptor gene cag polymorphism. *J Clin Endocrinol Metab* 2011;96(4):E739-45.
178. Ferreira I.M., I.T. Verreschi, L.E. Nery, R.S. Goldstein, N. Zamel, D. Brooks, J.R. Jardim. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest* 1998;114(1):19-28.
179. Ferreira U., V.A. Leitao, F. Denardi, W.E. Matheus, R.M. Stopiglia, N.R. Netto. Intermittent androgen replacement for intense hypogonadism symptoms in castrated patients. *Prostate Cancer Prostatic Dis* 2006;9(1):39-41.
180. Fiegel G., R. Bargheer, M. Heindorf, D. Kukwa. Metabolism activation in old age with vitamin and hormone substitution. *Therapiewoche* 1965;15:563.
181. Findlay J.C., V. Place, P.J. Snyder. Treatment of primary hypogonadism in men by the transdermal administration of testosterone. *J Clin Endocrinol Metabol* 1989;68(2):369-73.
182. Findlay J.C., V.A. Place, P.J. Snyder. Transdermal delivery of testosterone. *Journal of Clinical Endocrinology and Metabolism*. 1987;64(2):266.-8.
183. Finkle W.D., S. Greenland, G.K. Ridgeway, J.L. Adams, M.A. Frasco, M.B. Cook, J.F. Fraumeni, R.N. Hoover. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;9(1):e85805.
184. First gel for testosterone deficiency. *J Gender-Specific Med* 2001;4(2):6.
185. Fizazi, F. Lesaunier, R. Delva, G. Gravis, F. Rolland, F. Priou, J.M. Ferrero, N. Houed. A phase III trial of docetaxel-estradiol in high-risk localized prostate cancer: a planned analysis of response, toxicity and quality of life in the GETUG 12 trial. *Eur J Cancer* 2012;48(2):209-17.
186. Fomina L.G.. Use of sex hormones in patients with coronary atherosclerosis. *Terapevticheskie Arkhiv* 1968;40:43.
187. Foresta C., N. Caretta, A. Lana, Toni L. De, A. Biagioli, A. Ferlin, A. Garolla. Reduced number of circulating endothelial progenitor cells in hypogonadal men. *J Clin Endocrinol Metab* 2006;91(11):4599-602.
188. Frederiksen L., D. Grintborg, K. Hojlund, D.M. Hougaard, K. Brixen, L.M. Rasmussen, M. Andersen. Osteoprotegerin levels decrease during testosterone therapy in aging men and are associated with changed distribution of regional fat. *Horm Metab Res* 2013;45(4):308-13.
189. Frederiksen L., K. Hojlund, D.M. Hougaard, K. Brixen, M. Andersen. Testosterone therapy increased muscle mass and lipid oxidation in aging men. *Age (Dordr)* 2012;34(4):145-56.
190. Frederiksen L., K. Hojlund, D.M. Hougaard, T.H. Mosbech, R. Larsen, A. Flyvbjerg, J. Frystyk, K. Brixen, M. Andersen. Testosterone therapy decreases subcutaneous fat and adiponectin in aging men. *Eur J Endocrinol* 2012;166(3):469-76.
191. Friedl K.E., R.E. Jones, C.J. Hannan, S.R. Plymate. The administration of pharmacological doses of testosterone or 19-nortestosterone to normal men is not associated with increased insulin secretion or impaired glucose tolerance. *J Clin Endocrinol Metab* 1989;68(5):971-5.
192. Fukai S., M. Akishita, S. Yamada, K. Toba, Y. Ouchi. Effects of testosterone in older men with mild-to-moderate cognitive impairment. *J Am Geriatr Soc*. 2010;58(7):1419-21.
193. Gades N.M., D.J. Jacobson, M.E. McGree, J.L. St Sauver, M.M. Lieber, A. Nehra, C.J. Girman, G.G. Klee, S.J. Jacobsen. The associations between serum sex hormones, erectile function, and sex drive: the Olmsted County Study of Urinary Symptoms and Health Status among Men. *J Sex Med* 2008;5(9):2209-20.
194. Gao T., H. Cai, C. Wang. Observation of treatment with androgen supplement in partial androgen deficiency in the aging male accompanied with depression. *Chinese Journal of Andrology* 2006;20(1):46-8.
195. Gaylis F.D., D.W. Lin, J.M. Ignatoff, C.L. Amling, R.F. Tutrone, D.J. Cosgrove. Prostate cancer in men using testosterone supplementation. *J Urol* 2005;174:534.
196. Genazzani A.D., G. Forti, M. Maggi, M. Milloni, F. Cianfanelli, V. Guardabasso, V. Toscano, M. Serio, D. Rodbard. Pulsatile secretion of luteinizing hormone in agonadal men before and during testosterone replacement therapy. *J Endocrinol Invest* 1990;13(10):777-86.

197. Gentili A., T. Mulligan, M. Godschalk, J. Clore, J. Patrie, A. Iranmanesh, J.D. Veldhuis. Unequal impact of short-term testosterone repletion on the somatotrophic axis of young and older men. *J Clin Endocrinol Metab* 2002;87(2):825-34.
198. Gerstenbluth R.E., P.N. Maniam, E.W. Corty, A.D. Seftel. Prostate-specific antigen changes in hypogonadal men treated with testosterone replacement. *J Androl* 2002;23(6):922-6.
199. Giagulli V.A., L. Verdonck, J.P. Deslypere, R. Giorgino, A. Vermeulen. Comparison of plasma androgen glucuronide levels after percutaneous or peroral androgen treatment in men: evidence for important splanchnic contribution to plasma 17 beta-hydroxyandrogen glucuronides. *J Clin Endocrinol Metab* 1993;76(2):429-31.
200. Giagulli V.A., V. Triggiani, M.D. Carbone, G. Corona, E. Tafaro, B. Licchelli, E. Guastamacchia. The Role of Long-Acting Parenteral Testosterone Undecanoate Compound in the Induction of Secondary Sexual Characteristics in Males with Hypogonadotropic Hypogonadism. *J Sex Med* 2011;8(12):3471-8.
201. Giannoulis M.G., N. Jackson, F. Shojae-Moradie, K.S. Nair, P.H. Sonksen, F.C. Martin, A.M. Umpleby. The effects of growth hormone and/or testosterone on whole body protein kinetics and skeletal muscle gene expression in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 2008;93(8):3066-74.
202. Giannoulis M.G., N. Jackson, F. Shojae-Moradie, P.H. Sonksen, F.C. Martin, A.M. Umpleby. Effects of growth hormone and/or testosterone on very low density lipoprotein apolipoprotein B100 kinetics and plasma lipids in healthy elderly men: a randomised controlled trial. *Growth Horm IGF Res* 2006;16(5-6):308-17.
203. Giannoulis M.G., P.H. Sonksen, M. Umpleby, L. Breen, C. Pentecost, M. Whyte, C.V. McMillan, C. Bradley, F.C. Martin. The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 2006;91(2):477-84.
204. Gibney J., T. Wolthers, G. Johannsson, A.M. Umpleby, K.K. Ho. Growth hormone and testosterone interact positively to enhance protein and energy metabolism in hypopituitary men. *Am J Physiol Endocrinol Metab* 2005;289(2):E266-71.
205. Gilbert R.N., C.W. Graham, J.B. Regan. Double-blind- cross-over trial of testosterone enanthate in impotent men with low or low-normal serum testosterone levels. *J Urol* 1992;147:264.
206. Giltay E.J., A. Haider, F. Saad, L.J. Gooren. C-reactive protein levels and ageing male symptoms in hypogonadal men treated with testosterone supplementation. *Andrologia* 2008;40(6):398-400.
207. Ginzburg E., A. Lin, M. Sigler, D. Olsen, N. Klimas, A. Mintz. Testosterone and growth hormone normalization: a retrospective study of health outcomes. *J Multidiscip Healthc* 2008;1:79-86.
208. Ginzburg N., N. Klimas, C. Parvus, J. Life, R. Willix, M.J. Barber, A. Lin, F. Comite. Long-term safety of testosterone and growth hormone supplementation: a retrospective study of metabolic, cardiovascular, and oncologic outcomes. *J Clin Med Res* 2010;2(4):159-66.
209. Giorgi A., R.P. Weatherby, P.W. Murphy. Muscular strength, body composition and health responses to the use of testosterone enanthate: a double blind study. *J Sci Med Sport* 1999;2(4):341-55.
210. Giuberti A., S.C. Picozzi, L. Mazza, M. Casu, P. Vigano, V. Manganini, G.R. Strada. Testosterone supplementation in hypogonadal men: our personal experience. *Arch Ital Urol Androl* 2005;77(4):191-3.
211. Gleeson H.K., S.M. Shalet. Effect of aromatizable and unaromatizable androgen replacement in hypogonadal men on GH responsiveness. *Clin Endocrinol* 2009;70(1):109-15.
212. Glinborg D., L.L. Christensen, T. Kvorning, R. Larsen, K. Brixen, D.M. Hougaard, B. Richelsen, J.M. Bruun, M. Andersen. Strength training and testosterone treatment have opposing effects on migration inhibitor factor levels in ageing men. *Mediators Inflamm*. 2013;2013:539156.
213. Glueck C.J., C. Richardson-Royer, R. Schultz, T. Burger, D. Bowe, J. Padda, P. Wang. Testosterone therapy, thrombophilia-hypofibrinolysis, and hospitalization for deep venous thrombosis-pulmonary embolus: an exploratory, hypothesis-generating study. *Clin Appl Thromb Hemost* 2014;20(3):244-9.
214. Gluud C., J.H. Henriksen. Liver haemodynamics and function in alcoholic cirrhosis. Relation to testosterone treatment and ethanol consumption. *J Hepatol* 1987;4(2):168-73.
215. Gluud C., P. Bennett, B. Svenstrup, S. Micic. Effect of oral testosterone treatment on serum concentrations of sex steroids gonadotrophins and prolactin in alcoholic cirrhotic men. Copenhagen Study Group for Liver Diseases. *Aliment Pharmacol Ther* 1988;2(2):119-28.
216. Gluud C., P. Bennett, O. Dietrichson, S.G. Johnsen, L. Ranek, L.B. Svendsen, E. Juhl. Short-term parenteral and peroral testosterone administration in men with alcoholic cirrhosis. *Scand J Gastroenterol* 1981;16(6):749-55.
217. Gluud C., P. Christoffersen, J. Eriksen, P. Wantzin, B.B. Knudsen. No effect of long-term oral testosterone treatment on liver morphology in men with alcoholic cirrhosis. *Am J Gastroenterol* 1987;82(7):660-4.
218. Gluud C., P. Wantzin, J. Eriksen. No effect of oral testosterone treatment on sexual dysfunction in alcoholic cirrhotic men. *Gastroenterology*. 1988;95(6):1582-7.
219. Gold J., M.J. Batterham, H. Rekers, M.K. Harms, T.B. Geurts, P.M. Helmyr, Mendonca J. Silva de, L.H. Falleiros Carvalho, G. Panos, A. Pinchera, F. Aiuti, C. Lee, A. Horban, J. Gatell, P. Phanuphak, W. Prasithsirikul, B. Gazzard, M. Bloch, S.A. Danner, Investigators Study. Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. *HIV Med* 2006;7(3):146-55.
220. Goma A., M. Eissa, A. El-Gebaley. The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *Int J Impot Res* 2001;13(2):93-9.

221. Gooren L.J.. Long-term safety of the oral androgen testosterone undecanoate. *International J Androl* 1986;9(1):21-6.
222. Greenfield D.M., S.J. Walters, R.E. Coleman, B.W. Hancock, R. Eastell, H.A. Davies, J.A. Snowden, L. DeRogatis, S.M. Shalet, R.J. Ross. Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. *J Clin Endocrinol Metab* 2007;92(9):3476-82.
223. Greenstein, N.J. Mabjeesh, M. Sofer, I. Kaver, H. Matzkin, J. Chen. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? *J Urol* 2005;173(2):530-2.
224. Gregory J.W., S.A. Greene, J. Thompson, C.M. Scrimgeour, M.J. Rennie. Effects of oral testosterone undecanoate on growth, body composition, strength and energy expenditure of adolescent boys. *Clinical Endocrinology*. 1992/09//. 37:207
225. Griebling T.L. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Urol* 2011;185(2):641.
226. Griebling T.L.. Re: Low testosterone concentrations and the symptoms of testosterone deficiency according to the androgen deficiency in ageing males (ADAM) and ageing males' symptoms rating scale (AMS) questionnaires. *J Urol* 2012;187(2):624-5.
227. Griggs R.C., S. Pandya, J.M. Florence, M.H. Brooke, W. Kingston, J.P. Miller, J. Chutkow, B.E. Herr, R.T. Moxley. Randomized controlled trial of testosterone in myotonic dystrophy. *Neurology*. 1989;39(2 Pt 1):219-22.
228. Griggs R.C., W. Kingston, R.F. Jozefowicz, B.E. Herr, G. Forbes, D. Halliday. Effect of testosterone on muscle mass and muscle protein synthesis. *J Appl Physiol* 1989;66(1):498-503.
229. Grinspoon S., C. Corcoran, E. Anderson, J. Hubbard, T. Stanley, N. Basgoz, A. Klibanski. Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. *Clin Infect Dis* 1999;28(3):634-6.
230. Grinspoon S., C. Corcoran, T. Stanley, L. Katznelson, A. Klibanski. Effects of androgen administration on the growth hormone-insulin-like growth factor I axis in men with acquired immunodeficiency syndrome wasting. *J Clin Endocrinol Metab* 1998;83(12):4251-6.
231. Grober E.D., M. Khera, S.D. Soni, M.G. Espinoza, L.I. Lipshultz. Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. *Int J Impot Res* 2008;20(2):213-7.
232. Grossmann M., M.C. Thomas, S. Panagiotopoulos, K. Sharpe, R.J. MacIsaac, S. Clarke, J.D. Zajac, G. Jerums. Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* 2008;93(5):1834-40.
233. Gu Y.Q., Z.Y. Ge, G.Y. Zhang, W.J. Bremner. Quantitative and qualitative changes in serum luteinizing hormone after injectable testosterone undecanoate treatment in hypogonadal men. *Asian J Androl* 2000;2(1):65-71.
234. Guay A.T., J. Jacobson, J.B. Perez, M.B. Hodge, E. Velasquez. Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? *Int J Impot Res* 2003;15(3):156-65.
235. Guay A.T., T.M. Smith, L.A. Offutt. Absorption of testosterone gel 1% (Testim) from three different application sites. *J Sex Med* 2009;6(9):2601-10.
236. Guerrini P., R. Morville, G. Laborit. Role of testicle in the endocrine response to injury. Trial of early androgen treatment. *Revue Francaise d'Endocrinologie Clinique - Nutrition et Metabolisme* 1979;20(3):284.
237. Guler N., T. Batyraliev, H. Dulger, C. Ozkara, M. Tuncer, S. Aslan, H. Okut, M. Agirbasli. The effects of short term (3 weeks) testosterone treatment on serum inflammatory markers in men undergoing coronary artery stenting. *Int J Cardiol* 2006;109(3):339-43.
238. Guo C.Y., T.H. Jones, R. Eastell. Treatment of isolated hypogonadotropic hypogonadism effect on bone mineral density and bone turnover. *J Clin Endocrinol Metab* 1997;82(2):658-65.
239. Gupta S.K., E.A. Lindemulder, G. Sathyan. Modeling of circadian testosterone in healthy men and hypogonadal men. *J Clin Pharmacology* 2000;40(7):731-8.
240. H.G. Pope, R. Amiaz, B.P. Brennan, G. Orr, M. Weiser, J.F. Kelly, G. Kanayama, A. Siegel, J.I. Hudson, S.N. Seidman. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J Clin Psychopharmacol* 2010;30(2):126-34.
241. Habib F.K., M. Ross, R. Tate, G.D. Chisholm. Differential effect of finasteride on the tissue androgen concentrations in benign prostatic hyperplasia. *Clin Endocrinol* 1997;46(2):137-44.
242. Haider A., A. Yassin, G. Doros, F. Saad. Effects of long-term testosterone therapy on patients with "diabesity": results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes. *Int J Endocrinol* 2014;2014:683515
243. Haider A., L.J. Gooren, P. Padungtod, F. Saad. Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men. *Andrologia* 2009;41(1):7-13.
244. Haider A., L.J. Gooren, P. Padungtod, F. Saad. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. *Exp Clin Endocrinol Diabetes* 2010;118(3):167-71.

245. Haider A., U. Meergans, A. Traish, F. Saad, G. Doros, P. Lips, L. Gooren. Progressive improvement of T-Scores in men with osteoporosis and subnormal serum testosterone levels upon treatment with testosterone over six years. *Int J Endocrinol* 2014;2014:496948.
246. Hall G.M., J.P. Larbre, T.D. Spector, L.A. Perry, J.A. Da Silva. A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 1996;35(6):568-73.
247. Hall S.A., A.B. Araujo, G.R. Esche, R.E. Williams, R.V. Clark, T.G. Travison, J.B. McKinlay. Treatment of symptomatic androgen deficiency: results from the Boston Area Community Health Survey. *Arch Intern Med* 2008;168(10):1070-6.
248. Hana V., J. Marek, A. Mellanova, R. Hampl, L. Starka. Comparison of the effect of methyltestosterone and testosterone undecanoate in substitution therapy of hypogonadism. *Cas Lek Cesk* 1987;126:369.
249. Handelsman D.J., A.J. Conway, C.J. Howe, L. Turner, M.A. Mackey. Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot. *J Clin Endocrinol Metab* 1996;81(11):4113-21.
250. Handelsman D.J., M.A. Mackey, C. Howe, L. Turner, A.J. Conway. An analysis of testosterone implants for androgen replacement therapy. *Clin Endocrinol* 1997;47(3):311-6.
251. Hannan C.J., K.E. Friedl, A. Zold, T.M. Kettler, S.R. Plymate. Psychological and serum homovanillic acid changes in men administered androgenic steroids. *Psychoneuroendocrinology* 1991;16(4):335-43.
252. Haren M., I. Chapman, P. Coates, J. Morley, G. Wittert. Effect of 12 month oral testosterone on testosterone deficiency symptoms in symptomatic elderly males with low-normal gonadal status. *Age Ageing* 2005;34(2):125-30.
253. Haren M.T., G.A. Wittert, I.M. Chapman, P. Coates, J.E. Morley. Effect of oral testosterone undecanoate on visuospatial cognition, mood and quality of life in elderly men with low-normal gonadal status. *Maturitas* 2005;50(2):124-33.
254. Haring R., A. Teumer, U. Volker, M. Dorr, M. Nauck, R. Biffar, H. Volzke, S.E. Baumeister, H. Wallaschofski. Mendelian randomization suggests non-causal associations of testosterone with cardiometabolic risk factors and mortality. *Andrology* 2013;1(1):17-23.
255. Harkonen M., R. Pelkonen. Do male patients benefit from androgen replacement therapy? *Duodecim* 1996;112:1123.
256. Harman S.M., M.R. Blackman. The effects of growth hormone and sex steroid on lean body mass, fat mass, muscle strength, cardiovascular endurance and adverse events in healthy elderly women and men. *Horm Res* 2003;60(Suppl 1):121-4.
257. Hassan A., M. El-hadidy, B.S. El-deeck, T. Mostafa. Couple satisfaction to different therapeutic modalities for organic erectile dysfunction. *J Sex Med* 2008;5(10):2381-91.
258. He J., S. Bhasin, E.F. Binder, K.E. Yarasheski, C. Castaneda-Sceppa, E.T. Schroeder, R. Roubenoff, C.P. Chou, S.P. Azen, F.R. Sattler. Cardiometabolic risks during anabolic hormone supplementation in older men. *Obesity (Silver Spring)* 2013;21(5):968-75.
259. He X., G. Li, X. Zhang, H. Jiang, L. Zhao, D. Dai, Y. Xie. Clinical study of a small dose of androgen for the treatment of oligo-asthenospermia. *Chinese Journal of Andrology*. 2009;23(12):42.
260. He X., T. Song, G. Li, M. Yu, X. Wang, B. Hong. Clinical study of small doses androgen on the treatment of oligo-asthenospermia. *Chinese Journal of Andrology* 2006;20(7):28-32.
261. Henderson G.C., K. Dhatariya, G.C. Ford, K.A. Klaus, R. Basu, R.A. Rizza, M.D. Jensen, S. Khosla, P. O'Brien, K.S. Nair. Higher muscle protein synthesis in women than men across the lifespan, and failure of androgen administration to amend age-related decrements. *FASEB J* 2009;23(2):631-41.
262. Hobbs C.J., S.R. Plymate, C.J. Rosen, R.A. Adler. Testosterone administration increases insulin-like growth factor-I levels in normal men. *J Clin Endocrinol Metab* 1993;77(3):776-9.
263. Hogervorst E. Testosterone supplementation did not prevent cognitive decline or increase bone mineral density in older men. *Evid Based Med* 2008;13(3):71.
264. Hogervorst E., M. Combrinck, A.D. Smith. Testosterone and gonadotropin levels in men with dementia. *Neuro Endocrinol Lett* 2003;24(3-4):203-8.
265. Holmang S., P. Marin, G. Lindstedt, H. Hedelin. Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. *Prostate* 1993;23(2):99-106.
266. Howell S.J., J.A. Radford, J.E. Adams, E.M. Smets, R. Warburton, S.M. Shalet. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. *Clin Endocrinol* 2001;55(3):315-24.
267. Hoyos C.M., B.J. Yee, C.L. Phillips, E.A. Machan, R.R. Grunstein, P.Y. Liu. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. *Eur J Endocrinol* 2012;167:531-41.
268. Hoyos C.M., R. Killick, B.J. Yee, R.R. Grunstein, P.Y. Liu. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. *Clin Endocrinol* 2012;77(4):599-607.

269. Hsieh T.C., A.W. Pastuszak, K. Hwang, L.I. Lipshultz. Concomitant intramuscular human chorionic gonadotropin preserves spermatogenesis in men undergoing testosterone replacement therapy. *J Urol* 2013;189(2):647-50.
270. Huang G., S. Bhasin, E.R. Tang, A. Aakil, S.W. Anderson, H. Jara, M. Davda, T.G. Travison, S. Basaria. Re: Effect of testosterone administration on liver fat in older men with mobility limitation: Results from a randomized controlled trial. *J Urol* 2013;190(5):1840-1.
271. Huang X., M.R. Blackman, K. Herreman, K.M. Pabst, S.M. Harman, B. Caballero. Effects of growth hormone and/or sex steroid administration on whole-body protein turnover in healthy aged women and men. *Metabolism*. 2005;54(9):1162-7.
272. Hwang J.J., P.G. Dharmawardana, E.M. Uchio, J. Wynberg, J.L. Phillips. Prostate cancer in Klinefelter syndrome during hormonal replacement therapy. *Urology* 2003;62(5):941iv.
273. Ilani N., M.Y. Roth, J.K. Amory, R.S. Swerdloff, C. Dart, S.T. Page, W.J. Bremner, R. Sitruk-Ware, N. Kumar, D.L. Blithe, C. Wang. A new combination of testosterone and nesterone transdermal gels for male hormonal contraception. *Obstet Gynecol Sur* 2013;68(2):116-8.
274. Illig R., A. Prader. Effect of testosterone on growth hormone secretion in patients with anorchia and delayed puberty. *J Clin Endocrinol Metab* 1970;30(5):615-8.
275. In symptomatic androgen deficiency. Testosterone gel for rubbing in. *MMW Fortschritte der Medizin* 2003;145:57.
276. Increased risk of cardiovascular events associated with testosterone gel. *Aust J Pharm* 2011;92:90.
277. Ioannidis J.P.A.. Mega-trials for blockbusters. *JAMA* 2013;309(3):239-40.
278. Ip F.F., Pierro Di, R. Brown, I. Cunningham, D.J. Handelsman, P.Y. Liu. Trough serum testosterone predicts the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. *Eur J Endocrinol* 2010;162(2):385-90.
279. Isaia G., M. Mussetta, F. Pecchio, A. Sciolla, M. Di Stefano, G.M. Molinatti. Effect of testosterone on bone in hypogonadal males. *Maturitas* 1992;15(1):47-51.
280. Ishizaka K., M. Suzuki, Y. Kageyama, K. Kihara, K.-I. Yoshida. Bone mineral density in hypogonadal men remains low after long-term testosterone replacement. *Asian J Androl* 2002;4(2):117-21.
281. Islam N., A. Islam. Testosterone propionate in cirrhosis of the liver. *Br J Clin Pract* 1973;27(4):125-8.
282. Iudovskii S.O., A.S. Segal, D.I. Pushkar. Comparative characteristics of testosterone preparations for androgen-replacing therapy in male hypogonadism. *Urologiia* 2006;83.
283. J.B. Layton, D. Li, C.R. Meier, J.L. Sharpless, T. Sturmer, S.S. Jick, M.A. Brookhart. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *J Clin Endocrinol Metab* 2014;99:835-42.
284. Jaffe M.D.. Effect of testosterone cypionate on postexercise ST segment depression. *Br Heart J* 1977;39(11):1217-22.
285. Jakob E., V. Fuchs, R. Hoffmann, J. Keul. Physiological, hormonal and hematological changes in strenuous physical exercise under the influence of testosterone-enanthate. *Inter J Sports Med* 1988;9:401.
286. Jakobovits T.. The treatment of impotence with methyltestosterone thyroid (100 patients--double blind study). *Fertil Steril* 1970;21(1):32-5.
287. James J.S.. San Francisco area: testosterone replacement study, injection vs. patch. *AIDS Treat News* 1995;20(233):7-8.
288. Janowsky J.S., B. Chavez, E. Orwoll. Sex steroids modify working memory. *J Cogn Neurosci* 2000;12(3):407-14.
289. Jeong S.M., B.K. Ham, M.G. Park, M.M. Oh, D.K. Yoon, J.J. Kim, D.G. Moon. Effect of testosterone replacement treatment in testosterone deficiency syndrome patients with metabolic syndrome. *Korean J Urol* 2011;52(8):566-71.
290. Jick S.S., K.W. Hagberg. The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database. *Br J Clin Pharmacol* 2013;75(1):260-70.
291. Johannsson G., J. Gibney, T. Wolthers, K.C. Leung, K.K. Ho. Independent and combined effects of testosterone and growth hormone on extracellular water in hypopituitary men. *J Clin Endocrinol Metab* 2005;90(7):3989-94.
292. Johnsen S.G., E.P. Bennett, J. Gauno. Therapeutic effectiveness of oral testosterone. *Lancet* 1974;2:1473.
293. Johnson C.A.. Use of androgens in patients with renal failure. *Semin Dial* 2000;13(1):36-9.
294. Johnson H.R., S.A. Myhre, R.H. Ruvalcaba, H.C. Thuline, V.C. Kelley. Effects of testosterone on body image and behavior in Klinefelter's syndrome: a pilot study. *Dev Med Child Neurol* 1970;12(4):454-60.
295. Jordan W.P., L.E. Atkinson, C. Lai. Comparison of the skin irritation potential of two testosterone transdermal systems: an investigational system and a marketed product. *Clin Ther* 1998;20(1):80-7.
296. Jordan W.P.. Allergy and topical irritation associated with transdermal testosterone administration: a comparison of scrotal and nonscrotal transdermal systems. *Am J Contact Dermat* 1997;8(2):108-13.
297. Jorgensen J.O.L., N. Vahl, T.B. Hansen, C. Skjaerbaek, S. Fisker, H. Orskov, C. Hagen, J.S. Christiansen. Determinants of serum insulin-like growth factor I in growth hormone deficient adults as compared to healthy subjects. *Clin Endocrinol* 1998;48(4):479-86.
298. Jungwirth A., E. Plas, P. Geurts. Clinical experience with Andriol Testocaps - The first Austrian surveillance study on the treatment of late-onset hypogonadism. *Aging Male* 2007;10(4):183-7.
299. Kai S., C. Xiangfeng, P. Ping. Significance of TSI in the diagnosis of late onset hypogonadism. *Chinese Journal of Andrology* 2011;25(8):47-9.

300. Kaiser E., N. Kies, G. Maass. The measurement of the psychotropic effects of an androgen in aging males with psychovegetative symptomatology: A controlled double blind study, mesterolone versus placebo. *Prog Neuro-Psychopharmacol* 1978;2(4):505-15.
301. Kalinchenko S.Y., G.I. Kozlov, N.P. Gontcharov, G.V. Katsiya. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male* 2003;6(2):94-9.
302. Kalinchenko S.Y., Y.A. Tishova, G.J. Mskhalaya, L.J. Gooren, E.J. Giltay, F. Saad. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: The double-blind placebo-controlled Moscow study. *J Urol* 2011;185(2):635.
303. Kaltwasser J.P., U. Dix, K.P. Schalk, H. Vogt. Effect of androgens on the response to antithymocyte globulin in patients with aplastic anaemia. *Eur J Haematol* 1988;40(2):111-8.
304. Kaminetsky J.C., B. Moclair, M. Hemani, M. Sand. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. *J Sex Med* 2011;8(4):1186-96.
305. Kamp, H.M. Conaglen, R. Paul, T. Yarndley, C. Barea, M.S. Elston, J.V. Conaglen. A study of the complications of testosterone undecanoate (Reandron) replacement therapy for male hypogonadism in a cohort of 214 men. *N Z Med J* 2011;124(1334):6.
306. Kaplan A.L., J.C. Hu. Use of testosterone replacement therapy in the United States and its effect on subsequent prostate cancer outcomes. *Urology* 2013;82(2):321-6.
307. Kaplan A.L., Q.D. Trinh, M. Sun, S.C. Carter, P.L. Nguyen, Y.C. Shih, L.S. Marks, J.C. Hu. Testosterone replacement therapy following the diagnosis of prostate cancer: outcomes and utilization trends. *J Sex Med* 2014;11(4):1063-70.
308. Kaplowitz P.. Delayed puberty in obese boys: comparison with constitutional delayed puberty and response to testosterone therapy. *J Pediatr* 1998;133(6):745-9.
309. Karamanolakis D., T. Lambou, J. Bogdanos, C. Milathianakis, A. Sourla, P. Lembessis, A. Halapas, N. Pissimissis, N. Dessypris, E.Th. Petridou, M. Koutsilieris. Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (>3.0 and <10.0 ng/ml). *Anticancer Res* 2006;26(4B):3159-66.
310. Karazindiyanoglu S., S. Cayan. The effect of testosterone therapy on lower urinary tract symptoms/bladder and sexual functions in men with symptomatic late-onset hypogonadism. *Aging Male* 2008;11(3):146-9.
311. Katznelson L., J.S. Finkelstein, D.A. Schoenfeld, D.I. Rosenthal, E.J. Anderson, A. Klibanski. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metabol* 1996;81(12):4358-65.
312. Katznelson L., M.W. Robinson, C.L. Coyle, H. Lee, C.E. Farrell. Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. *Eur J Endocrinol* 2006;155(6):867-75.
313. Kaufman J.M., R.J. Graydon. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol* 2004;172(3):920-2.
314. Kaufman J.M., M.G. Miller, S. Fitzpatrick, C. McWhirter, J.J. Brennan. One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: results of a 182-day open-label extension of a 6-month double-blind study. *J Sex Med* 2012;9(4):1149-61.
315. Kelleher S., A.J. Conway, D.J. Handelsman. Blood testosterone threshold for androgen deficiency symptoms. *J Clin Endocrinol Metab* 2004;89(8):3813-7.
316. Kelleher S., C. Howe, A.J. Conway, D.J. Handelsman. Testosterone release rate and duration of action of testosterone pellet implants. *Clin Endocrinol* 2004;60(4):420-8.
317. Kelleher S., L. Turner, C. Howe, A.J. Conway, D.J. Handelsman. Extrusion of testosterone pellets: a randomized controlled clinical study. *Clin Endocrinol* 1999;51(4):469-71.
318. Kempisty-Zdebik E., A. Zdebik. The importance of testosterone in the treatment of metabolic syndrome in men. *Przegląd Lekarski* 2012;69:29.
319. Kenny A.M., G. Fabregas, C. Song, B. Biskup, S. Bellantonio. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci* 2004;59(1):75-8.
320. Kenny A.M., K.M. Prestwood, C.A. Gruman, G. Fabregas, B. Biskup, G. Mansoor. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2002;57(7):M460-5.
321. Kenny A.M., K.M. Prestwood, C.A. Gruman, K.M. Marcello, L.G. Raisz. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2001;56(5):M266-72.
322. Kenny A.M., K.M. Prestwood, L.G. Raisz. Short-term effects of intramuscular and transdermal testosterone on bone turnover, prostate symptoms, cholesterol, and hematocrit in men over age 70 with low testosterone levels. *Endocr Res* 2000;26(2):153-68.
323. Kenny A.M., S. Bellantonio, C.A. Gruman, R.D. Acosta, K.M. Prestwood. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2002; 57(5):M321-5.

324. Khara M., D. Crawford, A. Morales, A. Salonia, A. Morgentaler. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol* 2014;65(1):115-23.
325. Khara M., E.D. Grober, B. Najari, J.S. Colen, O. Mohamed, D.J. Lamb, L.I. Lipshultz. Testosterone replacement therapy following radical prostatectomy. *J Sex Med* 2009;6(4):1165-70.
326. Khara M., R.K. Bhattacharya, G. Blick, H. Kushner, D. Nguyen, M.M. Miner. Changes in prostate specific antigen in hypogonadal men after 12 months of testosterone replacement therapy: Support for the prostate saturation theory. *J Urol* 2011;186(3):1005-11.
327. Khara M., R.K. Bhattacharya, G. Blick, H. Kushner, D. Nguyen, M.M. Miner. The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). *Aging Male* 2012;15(1):14-21.
328. Khara M., R.K. Bhattacharya, G. Blick, H. Kushner, D. Nguyen, M.M. Miner. Improved sexual function with testosterone replacement therapy in hypogonadal men: Real-world data from the Testim Registry in the United States (TRiUS). *J Sex Med* 2011;8(11):3204-13.
329. Kido Y., S. Sakazume, Y. Abe, Y. Oto, H. Itabashi, M. Shiraishi, A. Yoshino, Y. Tanaka, K. Obata, N. Murakami, T. Nagai. Testosterone replacement therapy to improve secondary sexual characteristics and body composition without adverse behavioral problems in adult male patients with Prader-Willi syndrome: an observational study. *Am J Med Genet A* 2013;161A(9):2167-73.
330. Killick R., D. Wang, C.M. Hoyos, B.J. Yee, R.R. Grunstein, P.Y. Liu. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomised, placebo-controlled trial. *J Sleep Res* 2013;22(3):331-6.
331. Knapp P.E., T.W. Storer, K.L. Herbst, A.B. Singh, C. Dzekov, J. Dzekov, M. LaValley, A. Zhang, J. Ulloor, S. Bhasin. Effects of a supraphysiological dose of testosterone on physical function, muscle performance, mood, and fatigue in men with HIV-associated weight loss. *Am J Physiol Endocrinol Metab* 2008;294(6):E1135-43.
332. Ko Y.H., Y.M. Lew, S.W. Jung, S.H. Joe, C.H. Lee, H.G. Jung, M.S. Lee. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2008;28(4):375-83.
333. Kocar I.H., Z. Yesilova, M. Ozata, M. Turan, A. Sengul, I. Ozdemir. The effect of testosterone replacement treatment on immunological features of patients with Klinefelter's syndrome. *Clin Exp Immunol* 2000;121(3):448-52.
334. Kohler T.S., J. Kim, K. Feia, J. Bodie, N. Johnson, A. Makhlof, M. Monga. Prevalence of androgen deficiency in men with erectile dysfunction. *Urology* 2008;71(4):693-7.
335. Korbonits M., M. Kipnes, A.B. Grossman. Striant SR: a novel, effective and convenient testosterone therapy for male hypogonadism. *Int J Clin Pract* 2004;58(11):1073-80.
336. Korbonits M., M. Slawik, D. Cullen, R. J. Ross, G. Stalla, H. Schneider, M. Reincke, P.M. Bouloux, A.B. Grossman. A comparison of a novel testosterone bioadhesive buccal system, striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrinol Metab* 2004;89(5):2039-43.
337. Korenman S.G., S. Viosca, D. Garza, M. Guralnik, V. Place, P. Campbell, S.S. Davis. Androgen therapy of hypogonadal men with transscrotal testosterone systems. *Am J Med* 1987;83(3):471-8.
338. Kouri E.M., H.G. Pope, P.S. Oliva. Changes in lipoprotein-lipid levels in normal men following administration of increasing doses of testosterone cypionate. *Clin J Sport Med* 1996;6(3):152-7.
339. Kouri E.M., S.E. Lukas, H.G. Pope, P.S. Oliva. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. *Drug Alcohol Depend* 1995;40(1):73-9.
340. Koutsari C, Ali AH, Nair KS, et al. Fatty acid metabolism in the elderly: effects of dehydroepiandrosterone and testosterone replacement in hormonally deficient men and women. *J Clin Endocrinol Metab* 2009;94:3414.
341. Kovac J.R., S. Rajanahally, R.P. Smith, R.M. Coward, D.J. Lamb, L.I. Lipshultz. Patient satisfaction with testosterone replacement therapies: the reasons behind the choices. *J Sex Med* 2014;11(2):553-62.
342. Kovary P.M., H. Lenau, H. Niermann, E. Zierden, H. Wagner. Testosterone levels and gonadotrophins in Klinefelter's patients treated with injections of mesterolone cypionate. *Arch Dermatol Res* 1977;258(3):289-94.
343. Kuhn J.M., M.H. Laudat, Lignieres B. de. Percutaneous androgen treatment of male hypogonadism. Comparison of the efficacy of testosterone and dihydrotestosterone. A study of 40 cases. *Contraception Fertilite Sexualite* 1986;14(11):1031-6.
344. Kumanov, A. Tomova, G. Kirilov. Testosterone replacement therapy in male hypogonadism is not associated with increase of endothelin-1 levels. *Int J Androl* 2007;30(1):41-7.
345. Kunelius P., O. Lukkarinen, M.L. Hannuksela, O. Itkonen, J.S. Tapanainen. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab* 2002;87(4):1467-72.
346. Kurbatov D., J. Kuznetsky, A. Traish. Testosterone improves erectile function in hypogonadal patients with venous leakage. *J Androl* 2008;29(6):630-7.
347. Kvorning, L.L. Christensen, K. Madsen, J.L. Nielsen, K.D. Gejl, K. Brixen, M. Andersen. Mechanical muscle function and lean body mass during supervised strength training and testosterone therapy in aging men with low-normal testosterone levels. *J Am Geriatr Soc* 2013;61(6):957-62.

348. Kwan M., W.J. Greenleaf, J. Mann, L. Crapo, J.M. Davidson. The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men. *J Clin Endocrinol Metabol* 1983;57(3):557-62.
349. La Fountaine M.F., J.M. Wecht, C.M. Ciriigliaro, S.C. Kirshblum, A.M. Spungen, W.A. Bauman. Testosterone replacement therapy improves QTaVI in hypogonadal men with spinal cord injury. *Neuroendocrinology* 2013;97(4):341-6.
350. Labady F. Treatment of testicular hypofunction with gonadotrophic hormones. *Int Urol Nephrol* 1978;10(2):125-30.
351. Laitinen E.-M., M. Hero, K. Vaaralahti, J. Tammiska, T. Raivio. Bone mineral density, body composition and bone turnover in patients with congenital hypogonadotropic hypogonadism. *Int J Androl* 2012;35(4):534-40.
352. Lakshman K.M., B. Kaplan, T.G. Travison, S. Basaria, P.E. Knapp, A.B. Singh, M.P. LaValley, N.A. Mazer, S. Bhasin. The effects of injected testosterone dose and age on the conversion of testosterone to estradiol and dihydrotestosterone in young and older men. *J Clin Endocrinol Metabol* 2010;95(8):3955-64.
353. Lambert C.P., D.H. Sullivan, S.A. Freeling, D.M. Lindquist, W.J. Evans. Effects of testosterone replacement and/or resistance exercise on the composition of megestrol acetate stimulated weight gain in elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 2002; 87(5):2100-6.
354. Lambert C.P., D.H. Sullivan, W.J. Evans. Effects of testosterone replacement and/or resistance training on interleukin-6, tumor necrosis factor alpha, and leptin in elderly men ingesting megestrol acetate: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2003;58(2):165-70.
355. Lambert C.P., D.H. Sullivan, W.J. Evans. Megestrol acetate-induced weight gain does not negatively affect blood lipids in elderly men: effects of resistance training and testosterone replacement. *J Gerontol A Biol Sci Med Sci* 2003;58(7):644-7.
356. Lambert C.P., M.G. Flynn, D.H. Sullivan, W.J. Evans. Effects of megestrol acetate on circulating interleukin-15 and interleukin-18 concentrations in healthy elderly men. *J Gerontol A Biol Sci Med Sci* 2004;59(8):855-8.
357. Lanfranco F., M. Zitzmann, M. Simoni, E. Nieschlag. Serum adiponectin levels in hypogonadal males: influence of testosterone replacement therapy. *Clin Endocrinol* 2004;60:500-7.
358. Lasaponara F., M. Paradiso, M.G. Milan, F. Morabito, O. Sedigh, M.E. Graziano, A. Abbona, G.B. Piccoli, M. Rossetti, E. Mezza, U. Ferrando. Erectile dysfunction after kidney transplantation: our 22 years of experience. *Transplant Proc* 2004;36(3):502-4.
359. LeBrasseur N.K., N. Lajevardi, R. Miciek, N. Mazer, T.W. Storer, S. Bhasin. Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM Trial): design and methods. *Contemp Clin Trials* 2009;30(2):133-40.
360. Leder B.Z., C. Longcope, D.H. Catlin, B. Ahrens, D.A. Schoenfeld, J.S. Finkelstein. Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000;283(6):779-82.
361. Lee C.-H., S.-W. Kuo, Y.-J. Hung, C.-H. Hsieh, C.-T. He, T.-C. Yang, W.-C. Lian, S. Chyi-Fan, D. Pei. The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics. *Endocr Res* 2005;31(2):139-48.
362. Lee K.K., N. Berman, G.M. Alexander, L. Hull, R.S. Swerdloff, C. Wang. A simple self-report diary for assessing psychosexual function in hypogonadal men. *J Androl* 2003;24(5):688-98.
363. Lee M.J., H.K. Ryu, S.Y. An, J.Y. Jeon, J.I. Lee, Y.S. Chung. Testosterone replacement and bone mineral density in male pituitary tumor patients. *Endocrinol Metab (Seoul)* 2014;29(1):48-53.
364. Legros J.J., E.J. Meuleman, J.M. Elbers, T.B. Geurts, M.J. Kaspers, P.M. Bouloux, Study 43203 Investigators. Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. *Eur J Endocrinol* 2009;160(5):821-31.
365. Leifke E., M. Kinzel, D. Tsikas, L. Gooren, J.C. Frolich, G. Brabant. Effects of normalization of plasma testosterone levels in hypogonadal men on plasma levels and urinary excretion of asymmetric dimethylarginine (ADMA). *Horm Metab Res* 2008;40(1):56-9.
366. Lemcke B., J. Zentgraf, H.M. Behre, S. Kliesch, J.H. Bramswig, E. Nieschlag. Long-term effects on testicular function of high-dose testosterone treatment for excessively tall stature. *J Clinical Endocrinol Metab* 1996;81(1):296-301.
367. Levien T.L., D.E. Baker. Reviews of fluvoxamine maleate and testosterone transdermal system. *Hosp Pharm* 1994;29(6):613-8.
368. Lewis M.I., M. Fournier, T.W. Storer, S. Bhasin, J. Porszasz, S.G. Ren, X. Da, R. Casaburi. Skeletal muscle adaptations to testosterone and resistance training in men with COPD. *J Appl Physiol* 2007;103(4):1299-310.
369. Li G.Y., J.H. Liang, Z.B. Meng, C.C. Huang, S.K. Liang, G.Q. Wei, S.L. Shen, C.H. Zhu, X. Zhang, W.R. Song. Low-dose testosterone undecanoate capsules combined with tadalafil for late-onset hypogonadism accompanied with ED. *Zhonghua Nan Ke Xue* 2013;19:630.
370. Li J.Y., J.C. Zhu, J.T. Dou, W.J. Bai, S.M. Deng, M. Li, W. Huang, H. Jin. Effects of androgen supplementation therapy on partial androgen deficiency in the aging male: a preliminary study. *Aging Male* 2002;5(1):47-51.
371. Liao C.-H., Y.-N. Wu, F.-Y. Lin, W.-K. Tsai, S.-P. Liu, H.-S. Chiang. Testosterone replacement therapy can increase circulating endothelial progenitor cell number in men with late onset hypogonadism. *Andrology* 2013;1(4):563-9.
372. Lim L.S., P.Y. Takahashi. Osteoporosis intervention in men with hip fracture. *Age Ageing* 2004; 33(5):507-8.

373. Liu P.Y., B. Yee, S.M. Wishart, M. Jimenez, D.G. Jung, R.R. Grunstein, D.J. Handelsman. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metabol* 2003;88(8):3605-13.
374. Liu P.Y., C. Wang, R.S. Swerdloff. Does individual response to androgen replacement therapy affect bone density? *Nature Clin Pract Endocrinol Metab* 2006;2(2):76-7.
375. Lofthouse. New testosterone transdermal delivery system is effective in healthy men. *Nat Clin Pract Endocrinol Metab* 2006;2(6):304-5.
376. Long-term sequelae of sex steroid treatment for tall stature. *Eur J Pediatr* 1996;155(7):617-8.
377. Lovejoy J.C., G.A. Bray, C.S. Greeson, M. Klemperer, J. Morris, C. Partington, R. Tulley. Oral anabolic steroid treatment, but not parenteral androgen treatment, decreases abdominal fat in obese, older men. *Int J Obes Relat Metab Disord* 1995;19(9):614-24.
378. Lu J., SJ, J. Fan, J. Zhu, G.M. Lin. The prospective and randomized control study of Viagra combined with Andriol in the treatment of ED in the aging male. *Chinese Journal of Andrology* 2003;17:194.
379. Lu P.H., D.A. Masterman, R. Mulnard, C. Cotman, B. Miller, K. Yaffe, E. Reback, V. Porter, R. Swerdloff, J.L. Cummings. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol* 2006;63(2):177-85.
380. Luboshitzky R., O. Wagner, S. Lavi, P. Herer, P. Lavie. Abnormal melatonin secretion in hypogonadal men: the effect of testosterone treatment. *Clin Endocrinol* 1997;47(4):463-9.
381. Lubushitzky R., D. Front, G. Iosilevsky, L. Bettman, A. Frenkel, G.M. Kolodny, O. Israel. Quantitative bone SPECT in young males with delayed puberty and hypogonadism: implications for treatment of low bone mineral density. *J Nucl Med* 1998;39(1):104-7.
382. Lufkin E.G., F.B. Stifel, R.H. Herman, N.S. Rosensweig. Effect of testosterone on jejunal pyruvate kinase activities in normal and hypogonadal males. *J Clin Endocrinol* 1972;34(3):586-91.
383. Ly L.P., M. Jimenez, T.N. Zhuang, D.S. Celermajer, A.J. Conway, D.J. Handelsman. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. *J Clin Endocrinol Metab* 2001;86(9):4078-88.
384. MacIndoe J.H., P.J. Perry, W.R. Yates, T.L. Holman, V.L. Ellingrod, S.D. Scott. Testosterone suppression of the HPT axis. *J Investig Med* 1997;45(8):441-7.
385. MacNeil J.S. Intermittent androgen therapy shaves years off survival. *Oncology Report* 2012;July:12
386. Maggio M., F. Nicolini, C. Cattabiani, C. Beghi, T. Gherli, R.S. Schwartz, G. Valenti, G.P. Ceda. Effects of testosterone supplementation on clinical and rehabilitative outcomes in older men undergoing on-pump CABG. *Contemp Clin Trials* 2012;33(4):730-8.
387. Maggio M., P.J. Snyder, G.P. Ceda, Y. Milaneschi, M. Luci, C. Cattabiani, S. Masoni, A. Vignali, R. Volpi, F. Lauretani, H. Peachey, G. Valenti, A.R. Cappola, D. Longo, L. Ferrucci. Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. *Andrology* 2013;1(1):24-8.
388. Mahabadi V., J.K. Amory, R.S. Swerdloff, W.J. Bremner, S.T. Page, R. Sitruk-Ware, P.D. Christensen, N. Kumar, Y.-Y. Tsong, D. Blithe, C. Wang. Combined transdermal testosterone gel and the progestin nesterone suppresses serum gonadotropins in men. *Obstet Gynecol Sur* 2010;65(2) :105-6.
389. Malkin C.J., P.D. Morris, P.J. Pugh, K.M. English, K.S. Channer. Effect of testosterone therapy on QT dispersion in men with heart failure. *Am J of Cardiol* 2003;92(10):1241-3.
390. Malkin C.J., P.J. Pugh, J.N. West, E.J. van Beek, T.H. Jones, K.S. Channer. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006;27(1):57-64.
391. Malkin C.J., P.J. Pugh, P.D. Morris, K.E. Kerry, R.D. Jones, T.H. Jones, K.S. Channer. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart* 2004;90(8):871-6.
392. Malkin C.J., P.J. Pugh, R.D. Jones, D. Kapoor, K.S. Channer, T.H. Jones. The effect of testosterone replacement of endogenous inflammatory cytokines and lipid profiles in hypodondal men. *J Clin Endocrinol Metabol* 2004;89(7):3313-8.
393. Malkin C.J., T.H. Jones, K.S. Channer. The effect of testosterone on insulin sensitivity in men with heart failure. *Eur J Heart Fail* 2007;9(1):44-50.
394. Mao J.F., X.Y. Wu, N.S. Li, S.Y. Lu, Z.M. Jing, Y.F. Shi. Testosterone replacement in hypogonadotropic hypogonadal young male improves insulin sensitivity. *Chung Hua I Hsueh Tsa Chih* 2008;88:2550.
395. Marbury T., E. Hamill, R. Bachand, T. Seebree, T. Smith. Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim, compared to AndroGel. *Biopharm Drug Dispos* 2003;24(3):115-20.
396. Marin P., M. Krotkiewski, P. Bjorntorp. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. *Eur J Med* 1992;1(6):329-36.
397. Marin P., S. Holmang, C. Gustafsson, L. Jonsson, H. Kvist, A. Elander, J. Eldh, L. Sjostrom, G. Holm, P. Bjorntorp. Androgen treatment of abdominally obese men. *Obes Res* 1993;1(4):245-51.
398. Marin P., S. Holmang, L. Jonsson, L. Sjostrom, H. Kvist, G. Holm, G. Lindstedt, P. Bjorntorp. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 1992;16(12):991-7.
399. Marin P.. Testosterone and regional fat distribution. *Obes Res* 1995;3(Suppl 4):609S-612S.
400. Marin P.. Testosterone and regional fat distribution. *Obesity Res* 1995;3(Suppl 4):609S.

401. Martin M.M., A.L. Martin, K.L. Mossman. Testosterone treatment of constitutional delay in growth and development: effect of dose on predicted versus definitive height. *Acta Endocrinol Suppl (Copenh)*. 1986;279:147-52, 1986. #pages#
402. Masala A., R. Faedda, S. Alagna, A. Satta, G. Chiarelli, P.P. Rovasio, R. Ivaldi, M.S. Taras, E. Lai, E. Bartoli. Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997;126(4):292-5.
403. Masserot-Lureau C., N. Adoui, F. Degos, Bazelaire C. de, J. Soulier, S. Chevret, G. Socie, T. Leblanc. Incidence of liver abnormalities in Fanconi anemia patients. *Am J Hematol* 2012;87(5):547-9.
404. Mattern, C. Hoffmann, J.E. Morley, C. Badiu. Testosterone supplementation for hypogonadal men by the nasal route. *Aging Male* 2008;11(4):171-8.
405. Matthiesson K.L., P.G. Stanton, L. O'Donnell, S.J. Meachem, J.K. Amory, R. Berger, W.J. Bremner, R.I. McLachlan. Effects of testosterone and levonorgestrel combined with a 5alpha-reductase inhibitor or gonadotropin-releasing hormone antagonist on spermatogenesis and intratesticular steroid levels in normal men. *J Clin Endocrinol Metab* 2005;90(10):5647-55.
406. Mazer N., D. Bell, J. Wu, J. Fischer, M. Cosgrove, B. Eilers, R.N. BS. Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. *J Sex Med* 2005;2(2):213-26.
407. McClellan K.J., K.L. Goa. Transdermal testosterone. *Drugs*. 1998;55(2):253-8.
408. McLaren D., D.R. Siemens, J. Izard, A. Black, A. Morales. Clinical practice experience with testosterone treatment in men with testosterone deficiency syndrome. *BJU Int* 2008;102(9):1142-6.
409. Medras M., E.A. Jankowska, E. Rogucka. Effects of long-term testosterone substitutive therapy on bone mineral content in men with hypergonadotrophic hypogonadism. *Andrologia* 2001;33(1):47-52.
410. Mehtiyev T. The use of drugs Impaza and Nebido in the treatment of erectile dysfunction in patients with type 2 diabetes mellitus of reproductive age. *Georgian Med* 2013:61.
411. Meier C., P.Y. Liu, L.P. Ly, J. de Winter-Modzelewski, M. Jimenez, D.J. Handelsman, M.J. Seibel. Recombinant human chorionic gonadotropin but not dihydrotestosterone alone stimulates osteoblastic collagen synthesis in older men with partial age-related androgen deficiency. *J Clin Endocrinol Metab* 2004;89(6):3033-41.
412. Meikle A.W., D. Matthias, A.R. Hoffman. Transdermal testosterone gel: pharmacokinetics, efficacy of dosing and application site in hypogonadal men. *BJU Int* 2004;93(6):789-95.
413. Meikle A.W., N.A. Mazer, J.F. Moellmer, J.D. Stringham, K.G. Tolman, S.W. Sanders, W.D. Odell. Enhanced transdermal delivery of testosterone across nonscrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. *J Clin Endocrinol Metab* 1992;74(3):623-8.
414. Meikle A.W., S. Arver, A.S. Dobs, S.W. Sanders, L. Rajaram, N.A. Mazer. Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site- a clinical research center study. *J Clin Endocrinol Metab* 1996;81(5):1832-40.
415. Meriggola M.C., A. Costantino, S. Cerpolini, W.J. Bremner, D. Huebler, A.M. Morselli-Labate, B. Kirsch, A. Bertaccini, C. Pelusi, G. Pelusi. Testosterone undecanoate maintains spermatogenic suppression induced by cyproterone acetate plus testosterone undecanoate in normal men. *J Clin Endocrinol Metab* 2003;88(12):5818-26.
416. Meriggola M.C., A. Costantino, W.J. Bremner, A.M. Morselli-Labate. Higher testosterone dose impairs sperm suppression induced by a combined androgen-progestin regimen. *J Androl* 2002; 23(5):684-90.
417. Meriggola M.C., S. Marcovina, C.A. Paulsen, W.J. Bremner. Testosterone enanthate at a dose of 200 mg/week decreases HDL-cholesterol levels in healthy men. *Int J Androl* 1995;18(5):237-42.
418. Merza Z., A. Blumsohn, P.M. Mah, D.M. Meads, S.P. McKenna, K. Wylie, R. Eastell, F. Wu, R.J. Ross. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl*. 2006;29(3):381-91.
419. Miller J., M. Britto, S. Fitzpatrick, C. McWhirter, S.A. Testino, J.J. Brennan, T.L. Zimbrunnen. Pharmacokinetics and relative bioavailability of absorbed testosterone after administration of a 1.62% testosterone gel to different application sites in men with hypogonadism. *Endocr Pract* 2011;17(4):574-83.
420. Miner M.M., M. Khera, R.K. Bhattacharya, G. Blick, H. Kushner. Baseline data from the TRiUS registry: symptoms and comorbidities of testosterone deficiency. *Postgrad Med* 2011;123(3):17-27.
421. Miner M.M., R.K. Bhattacharya, G. Blick, H. Kushner, M. Khera. 12-month observation of testosterone replacement effectiveness in a general population of men. *Postgrad Med* 2013;125(2):8-18.
422. Minnemann T., M. Schubert, D. Hubler, I. Gouni-Berthold, S. Freude, C. Schumann, M. Oettel, M. Ernst, U. Mellinger, F. Sommer, W. Krone, F. Jockenhovel. A four-year efficacy and safety study of the long-acting parenteral testosterone undecanoate. *Aging Male* 2007;10(3):155-158.
423. Mirahmadi M.K., N.D. Vaziri, J.T. Gormon. Controlled evaluation of hemodialysis patients on nandrolone decanoate (ND) vs testosterone enanthate (TE) (androgens and dialysis patient). *Trans Am Soc Artif Organs* 1979;25:449.
424. Mitchell E., D. Thomas, R. Burnet. Testosterone improves motor function in Parkinson's disease. *Journal of Clinical Neuroscience*. 2006;13(1):133-6.
425. Mitkov M.D., I.Y. Aleksandrova, M.M. Orbetzova. Effect of transdermal testosterone or alpha-lipoic acid on erectile dysfunction and quality of life in patients with type 2 diabetes mellitus. *Folia Med (Plovdiv)*. 2013;55(1):55-60.

426. Moisey R., J. Swinburne, S. Orme. Serum testosterone and bioavailable testosterone correlate with age and body size in hypogonadal men treated with testosterone undecanoate (1000 mg IM--Nebido). *Clin Endocrinol* 2008;69(4):642-7.
427. Monga M., M. Kostelec, M. Kamarei. Patient satisfaction with testosterone supplementation for the treatment of erectile dysfunction. *Arch Androl* 2002;48(6):433-42.
428. Moon du G., M.G. Park, S.W. Lee, K. Park, J.K. Park, S.W. Kim, N.C. Park, T.Y. Ahn, J.S. Paick, J.T. Seo, D.Y. Yang, J.Y. Lee, J.J. Kim. The efficacy and safety of testosterone undecanoate (Nebido(R)) in testosterone deficiency syndrome in Korean: a multicenter prospective study. *J Sex Med* 2010; 7(6):2253-60.
429. Moore C., D. Huebler, T. Zimmermann, L.A.J. Heinemann, F. Saad, D.M. Thai. The Aging Males' Symptoms Scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urology* 2004;46(1):80-7.
430. Moraes J.B. de, R. Tardy. Clinical trial of the medicinal combination composed of gamma-aminobutyric acid with methyltestosterone, used in the treatment of psychoneuroendocrine disorders. *Hospital (Rio J)* 1965;68:1423.
431. Morales A., A.M. Black, L.E. Emerson. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int* 2009;103(1):62-4.
432. Morales A., B. Johnston, J.W. Heaton, A. Clark. Oral androgens in the treatment of hypogonadal impotent men. *J Urol* 1994;152(4):1115-8.
433. Morales A., E. Nieschlag, M. Schubert, A.A. Yassin, M. Zitzmann, M. Oettel. Clinical experience with the new long-acting injectable testosterone undecanoate. Report on the educational symposium on the occasion of the 5th World Congress on the Aging Male, 9-12 February 2006, Salzburg, Austria. *Aging Male* 2006;9(4):221-7.
434. Morgentaler A., A.S. Dobs, J.M. Kaufman, M.M. Miner, R. Shabsigh, R.S. Swerdloff, C. Wang. Long acting testosterone undecanoate therapy in men with hypogonadism: results of a pharmacokinetic clinical study. *J Urol* 2008;180(6):2307-13.
435. Morgentaler A., E.L. Rhoden. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. *Urology* 2006;68(6):1263-7.
436. Morgentaler A., R. Kacker. Andrology: Testosterone and cardiovascular risk-deciphering the statistics. *Nat Rev Urol* 2014;11(3):131-2.
437. Morgunov L.I., A.L. Vertkin, D.I. Pushkar. Safety of long-term replacement hormonal therapy in patients with erectile dysfunction and androgen deficiency. *Urologia* 2007;49.
438. Morgunov L.I., I.A. Denisova, T.I. Rozhkova, L.V. Stakhovskaia, V.I. Skvortsova. Androgenic deficit and its treatment in stroke male patients with diabetes mellitus type II. *Zh Nevrol Psikhiatr Im S S Korsakova* 2011;111:21.
439. Mori P.G., F. Cottafava, G. Vignola, A. Fossati-Guglielmoni. Idiopathic marrow aplasia. Long-term evaluation of androgen therapy. *Minerva Pediatrica* 1969;21:1561.
440. Morley J.E., H.M. Perry, F.E. Kaiser, D. Kraenzle, J. Jensen, K. Houston, M. Mattammal, Jr Perry. Effects of testosterone replacement therapy in old hypogonadal males: A preliminary study. *J Age Rel Disord* 1994;6(1):18-23.
441. Morley J.E., H.M. Perry, F.E. Kaiser, D. Kraenzle, J. Jensen, K. Houston, M. Mattammal, H.M. Perry. Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc* 1993;41(2):149-52.
442. Morris M.J., D. Huang, W.K. Kelly, S.F. Slovin, R.D. Stephenson, C. Eicher, A. Delacruz, T. Curley, L.H. Schwartz, H.I. Scher. Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer. *European Urology*. 2009;56(2):237-44.
443. Morrison B.F., M. Reid, W. Madden, A.L. Burnett. Testosterone replacement therapy does not promote priapism in hypogonadal men with sickle cell disease: 12-month safety report. *Andrology* 2013;1(4):576-82.
444. Morrow L.B., G.N. Burrow, S.R. Kaplan, P.J. Mulrow. Adrenal function in patients treated with testosterone and fluorinated pyrimidines. *J Clin Endocrinol Metab* 1968;28(2):308-10.
445. Moskovic D.J., D.J. Katz, A. Akhavan, K. Park, J.P. Mulhall. Clomiphene citrate is safe and effective for long-term management of hypogonadism. *BJU Int* 2012;110(10):1524-8.
446. Moskovic D.J., R.E. Freundlich, P. Yazdani, L.I. Lipshultz, M. Khera. Subcutaneous implantable testosterone pellets overcome noncompliance in adolescents with Klinefelter syndrome. *J Androl* 2012;33(4):570-3.
447. Mseddi S. Hadiji, L. Kammoun, H. Bellaaj, Youssef Y. Ben, L. Aissaoui, L. Torjemane, F. Telmoudi, A. Amouri, H. Elghezal, M. Ouederni, Abdennebi Y. Ben, S. Hammemi, Othmen T. Ben, Abid H. Ben, M. Bejaoui, S. Abdelhak, M. Hachicha, K. Dellagi, M. Frikha, le Group. Creation and report of the Tunisian Fanconi Anemia Registry (TFAR). *Archives de P,diatrie* 2012;19:467.
448. Mulligan K., R. Zackin, J.H. Von Roenn, M.A. Chesney, M.J. Egorin, F.R. Sattler, C.A. Benson, T. Liu, T. Umbleja, S. Shriver, R.J. Auchus, M. Schambelan, ACTG313 Study Team. Testosterone supplementation of megestrol therapy does not enhance lean tissue accrual in men with human immunodeficiency virus-associated weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. *J Clin Endocrinol Metab* 2007;92(2):563-70.
449. Muniyappa R., J.D. Sorkin, J.D. Veldhuis, S.M. Harman, T. Munzer, S. Bhasin, M.R. Blackman. Long-term testosterone supplementation augments overnight growth hormone secretion in healthy older men. *Am J Physiol Endocrinol Metab* 2007;293(3):E769-75.

450. Muniyappa R., J.D. Veldhuis, S.M. Harman, J.D. Sorkin, M.R. Blackman. Effects of testosterone administration on nocturnal cortisol secretion in healthy older men. *J Gerontol A Biol Sci Med Sci* 2010;65(11):1185-92.
451. Muniyappa R., K.A. Wong, H.L. Baldwin, J.D. Sorkin, M.L. Johnson, S. Bhasin, S.M. Harman, M.R. Blackman. Dehydroepiandrosterone secretion in healthy older men and women: effects of testosterone and growth hormone administration in older men. *J Clin Endocrinol Metab* 2006;91(11):4445-52.
452. Munzer T., C.J. Rosen, S.M. Harman, K.M. Pabst, Clair C. St, J.D. Sorkin, M.R. Blackman. Effects of GH and/or sex steroids on circulating IGF-I and IGFBPs in healthy, aged women and men. *Am J Physiol Endocrinol Metab* 2006;290(5):E1006-13/
453. Munzer T., S.M. Harman, J.D. Sorkin, M.R. Blackman. Growth hormone and sex steroid effects on serum glucose, insulin, and lipid concentrations in healthy older women and men. *J Clin Endocrinol Metab* 2009;94(10):3833-41.
454. Munzer T., S.M. Harman, P. Hees, E. Shapiro, C. Christmas, M.F. Bellantoni, T.E. Stevens, K.G. O'Connor, K.M. Pabst, Clair C. St, J.D. Sorkin, M.R. Blackman. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. *J Clin Endocrinol Metab* 2001;86(8):3604-10.
455. Mydlo J.H., R. Viterbo, P. Crispen. Use of combined intracorporal injection and a phosphodiesterase-5 inhibitor therapy for men with a suboptimal response to sildenafil and/or vardenafil monotherapy after radical retropubic prostatectomy. *BJU Int* 2005;95(6):843-6.
456. Nair KS, Rizza RA, O'Brien P, et al., DHEA in elderly women and DHEA or testosterone in elderly men. *NEJM* 2006;355:1647.
457. Nakhai Pour H.R., M.H. Emmelot-Vonk, M. Sukel-Helleman, H.J. Verhaar, D.E. Grobbee, Y.T. van der Schouw. Double blind randomized placebo-controlled trial on the effects of testosterone supplementation in elderly men with moderate to low testosterone levels: design and baseline characteristics [ISRCTN23688581]. *Trials* 2006;7:24
458. Nankin H.R., T. Lin, J. Osterman. Chronic testosterone cypionate therapy in men with secondary impotence. *Fertil Steril* 1986;46(2):300-7.
459. Navarro M.A., C.M. Villabona, A. Blanco, J.M. Gomez, R.M. Bonnin, J. Soler. Salivary excretory pattern of testosterone in substitutive therapy with testosterone enanthate. *Fertil Steril* 1994;61(1):125-8.
460. Neff G.W., C.B. O'Brien, M. Montalbano, D. Meyer, A. De Dmanno, H. Muslu, K. Safdar, S. Kahn, S. Nishida, E.R. Schiff. Beneficial effects of topical testosterone replacement in patients with end-stage liver disease. *Dig Dis Sci* 2004;49(7-8):1186-9.
461. Neff G.W., C.B. O'Brien, N.J. Shire, A. DeManno, S. Kahn, E. Rideman, K. Safdar, J. Madariaga, S.R. Rudich. Topical testosterone treatment for chronic allograft failure in liver transplant recipients with recurrent hepatitis C virus. *Transplant Proc* 2004;36(10):3071-4.
462. Neff M.S., J. Goldberg, R.F. Slifkin, A.R. Eiser, V. Calamia, M. Kaplan, A. Baez, S. Gupta, N. Mattoo. A comparison of androgens for anemia in patients on hemodialysis. *N Engl J Med* 1981;304(15):871-5.
463. Ng M.K., P.Y. Liu, A.J. Williams, S. Nakhla, L.P. Ly, D.J. Handelsman, D.S. Celermaier. Prospective study of effect of androgens on serum inflammatory markers in men. *Arterioscler Thromb Vasc Biol* 2002;22(7):1136-41.
464. Nielsen, B. Pelsen, K. Sorensen. Follow-up of 30 Klinefelter males treated with testosterone. *Clin Genet* 1988;33(4):262-9.
465. Nieschlag E., D. Buchter, Eckardstein S. von, K. Abshagen, M. Simoni, H.M. Behre. Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men. *Clin Endocrinol* 1999;51(6):757-63.
466. Nieschlag E., E. Vorona, M. Wenk, A.-K. Hemker, A. Kamischke, M. Zitzmann. Hormonal male contraception in men with normal and subnormal semen parameters. *Int J Androl* 2011;34(6 Pt1):556-67.
467. Nieschlag E., H.J. Cueppers, W. Wiegelmann, E.J. Wickings. Bioavailability and LH suppressing effect of different testosterone preparations in normal and hypogonadal men. *Horm Res* 1976;7(3):138-45.
468. Nieschlag E., J. Mauss, A. Coert, P. Kicovic. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. *Acta Endocrinol* 1975;79(2):366-74.
469. Nishioka H., J. Haraoka. Hypopituitarism and anemia: effect of replacement therapy with hydrocortisone and/or levothyroxine. *Journal of Endocrinological Investigation*. 2005;28:528.
470. Noguchi K., M. Takeda, K. Saitoh, Y. Kinoshita, A. Iwasaki, M. Hosaka. Hypogonadotropic hypogonadism: diagnosis and treatment of 30 cases. *Japanese Journal of Fertility and Sterility* 1999;44(2):77-81.
471. Nordin B.E., D.H. Marshall, R.M. Francis, R.G. Crilly. The effects of sex steroid and corticosteroid hormones on bone. *J Steroid Biochem* 1981;15:171-4.
472. O'Carroll R., C. Shapiro, J. Bancroft. Androgens, behaviour and nocturnal erection in hypogonadal men: the effects of varying the replacement dose. *Clin Endocrinol* 1985;23(5):527-38.
473. O'Connor D.B., J. Archer, W.M. Hair, F.C. Wu. Activational effects of testosterone on cognitive function in men. *Neuropsychologia* 2001;39(13):1385-94.
474. O'Connor D.B., J. Archer, W.M. Hair, F.C. Wu. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. *Physiol Behav* 2002;75(4):557-66/
475. Okun M.S., B.L. Walter, W.M. McDonald, J.L. Tenover, J. Green, J.L. Juncos, M.R. DeLong. Beneficial effects of testosterone replacement for the nonmotor symptoms of Parkinson disease. *Arch Neurol* 2002;59(11):1750-3.

476. Okun M.S., H.H. Fernandez, R.L. Rodriguez, J. Romrell, M. Suelter, S. Munson, E.D. Louis, T. Mulligan, P.S. Foster, B.V. Shenal, S.J. Armaghani, C. Jacobson, S. Wu, G. Crucian. Testosterone therapy in men with Parkinson disease: results of the TEST-PD Study. *Arch Neurol* 2006;63(5):729-35.
477. Orr G. The efficacy of testosterone replacement in treating middle-aged hypogonadal men with dysthymia: parallel group, double blind randomized trial [NCT00260390]. *ClinicalTrials.gov* Available: <http://clinicaltrials.gov/ct2/show/NCT00260390>.
478. Overvad S., K. Bay, A. Bojesen, C.H. Gravholt. Low INSL3 in Klinefelter syndrome is related to osteocalcin, testosterone treatment and body composition, as well as measures of the hypothalamic-pituitary-gonadal axis. *Andrology* 2014;2:421.
479. Ozata M., G. Ozisik, S. Caglayan, Z. Yesilova, N. Bingol, M. Saglam, M. Turan, Z. Beyhan. Effects of gonadotropin and testosterone treatments on plasma leptin levels in male patients with idiopathic hypogonadotropic hypogonadism and Klinefelter's syndrome. *Horm Metab Res* 1998;30(5):266-71.
480. Ozata M., M. Bulur, Z. Beyhan, A. Sengul, M. Saglam, M. Turan, A. Corakci, Gundogan M. Ali. Effects of gonadotropin and testosterone treatments on prostate volume and serum prostate specific antigen levels in male hypogonadism. *Endocr J* 1997;44(5):719-24.
481. Page S.T., J.K. Amory, A.M. Matsumoto. Does testosterone supplementation improve health and function in elderly men? *Nat Clin Pract Endocrinol Metab* 2008;4(7):374-5.
482. Page S.T., K.L. Herbst, J.K. Amory, A.D. Coviello, B.D. Anawalt, A.M. Matsumoto, W.J. Bremner. Testosterone administration suppresses adiponectin levels in men. *J Androl* 2005;26(1):85-92.
483. Page S.T., L. Hirano, J. Gilchrist, M. Dighe, J.K. Amory, B.T. Marck, A.M. Matsumoto. Dutasteride reduces prostate size and prostate specific antigen in older hypogonadal men with benign prostatic hyperplasia undergoing testosterone replacement therapy. *J Urol* 2011;186(1):191-7.
484. Papadimas J., E. Bili, F. Papadopoulou, E. Spanos, B. Tarlatzis, B. Kokkas, G. Pangalos, J. Bontis, S. Mantalenakis. Testosterone undecanoate versus mesterolone in hypogonadal male patients. *Rev Clin Pharmacol Pharmacokinetics Int Ed* 1996;10(1)3-8.
485. Parker S., M. Armitage. Experience with transdermal testosterone replacement therapy for hypogonadal men. *Clin Endocrinol* 1999;50(1):57-62.
486. Parsons J.K., H.B. Carter, E.A. Platz, E.J. Wright, P. Landis, E.J. Metter. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev* 2005;14(9):2257-60.
487. Pastuszak A.W., A.M. Pearlman, G. Godoy, B.J. Miles, L.I. Lipshultz, M. Khera. Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *Int J Impot Res* 2013;25(1):24-8.
488. Pastuszak A.W., A.M. Pearlman, W.S. Lai, G. Godoy, K. Sathymoorthy, J.S. Liu, B.J. Miles, L.I. Lipshultz, M. Khera. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urology* 2013;190(2):639-44.
489. Pastuszak A.W., H. Mittakanti, J.S. Liu, L. Gomez, L.I. Lipshultz, M. Khera. Pharmacokinetic evaluation and dosing of subcutaneous testosterone pellets. *J Androl* 2012;33(5):927-37.
490. Patwardhan A.J., S. Eliez, B. Bender, M.G. Linden, A.L. Reiss. Brain morphology in Klinefelter syndrome: extra X chromosome and testosterone supplementation. *Neurology* 2000;54(12):2218-23.
491. Pearl J.A., D. Berhanu, N. Francois, P. Masson, S. Zargaroff, J. Cashy, K.T. McVary. Testosterone supplementation does not worsen lower urinary tract symptoms. *J Urol* 2013;190(5):1828-33.
492. Pechersky A.V., V.I. Mazurov, V.F. Semiglazov, A.I. Karpischenko, V.V. Mikhailichenko, A.V. Ushintsev. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. *Int J Androl* 2002;25(2):119-25.
493. Pelusi, A. Costantino, S. Cerpolini, G. Pelusi, M.C. Meriggola, R. Pasquali. A placebo-controlled, randomized clinical trial using testosterone undecanoate with injectable norethisterone enanthate: effect on anthropometric, metabolic and biochemical parameters. *Int J Androl* 2011; 34(6 Pt 1):548-55.
494. Perry P.J., W.R. Yates, R.D. Williams, A.E. Andersen, J.H. MacIndoe, B.C. Lund, T.L. Holman. Testosterone therapy in late-life major depression in males. *J Clin Psychiatry* 2002;63(12):1096-101.
495. Petit J.H., C. Gluck, W.S. Kiger III, D.L. Henry, C. Karasiewicz, J. Talcott, S. Berg, E. Holupka, I. Kaplan. Bicalutamide alone prior to brachytherapy achieves cytoreduction that is similar to luteinizing hormone-releasing hormone analogues with less patient-reported morbidity. *Urologic Oncology: Seminars and Original Investigations* 2008;26(4):372-7.
496. Pexman-Fieth C., H.M. Behre, A. Morales, N. Kan-Dobrosky, M.G. Miller. A 6-month observational study of energy, sexual desire, and body proportions in hypogonadal men treated with a testosterone 1% gel. *Aging Male* 2014;17(1):1-11.
497. Piantadosi, R. Visvanathan, V. Naganathan, P. Hunter, I.D. Cameron, K. Lange, J. Karnon, I.M. Chapman. The effect of testosterone and a nutritional supplement on hospital admissions in under-nourished, older people. *BMC Geriatr* 2011;11:66.
498. Pison C., N. Cano, C. Cherion, H. Roth, C. Pichard, D.I.R. Investigateurs. Effects of home pulmonary rehabilitation in patients with chronic respiratory failure and nutritional depletion. *Rev Mal Respir* 2004;21:573.
499. Pison C.M., N.J. Cano, C. Cherion, F. Caron, Court-Fortune, M.T. Antonini, J. Gonzalez-Bermejo, L. Meziane, L.C. Molano, J.P. Janssens, F. Costes, B. Wuyam, T. Similowski, B. Melloni, M. Hayot, J. Augustin, C. Tardif, H.

- Lejeune, H. Roth, C. Pichard, I.R.A.D. Investigators. Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. *Thorax* 2011;66(11):953-60.
500. Place V.A., K.C. Nichols. Transdermal delivery of testosterone with TESTODERM to provide a normal circadian pattern of testosterone. *Ann N Y Acad Sci* 1991;618:441-9.
 501. Poliwczak A.R., M. Tylińska, M. Broncel. Effect of short-term testosterone replacement therapy on heart rate variability in men with hypoandrogen-metabolic syndrome. *Pol Arch Med Wewn* 2013;123(9):467-73.
 502. Pope H.G., E.M. Kouri, J.I. Hudson. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. *Arch Gen Psychiatry* 2000;57(2):133-40.
 503. Pope H.G., G.H. Cohane, G. Kanayama, A.J. Siegel, J.I. Hudson. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003; 160(1):105-11.
 504. Pugh P.J., K.M. English, T.H. Jones, K.S. Channer. Testosterone: A natural tonic for the failing heart? *QJM* 2000;93(10):689-94.
 505. Pugh P.J., R.D. Jones, C.J. Malkin, J. Hall, J.E. Nettleship, K.E. Kerry, T.H. Jones, K.S. Channer. Physiologic testosterone therapy has no effect on serum levels of tumour necrosis factor-alpha in men with chronic heart failure. *Endocr Res* 2005;31(4):271-83.
 506. Pugh P.J., R.D. Jones, J.N. West, T.H. Jones, K.S. Channer. Testosterone treatment for men with chronic heart failure. *Heart* 2004;90(4):446-7.
 507. Pugh P.J., T.H. Jones, K.S. Channer. Acute haemodynamic effects of testosterone in men with chronic heart failure. *Eur Heart J* 2003;24(10):909-15.
 508. Puliyl M.M., G.P. Vyas, G.S. Mehta. Testosterone in the management of cirrhosis of the liver--a controlled study. *Aust N Z J Med* 1977;7(6):17-30.
 509. Puliyl M.M., G.P. Vyas, G.S. Mehta. Testosterone in the management of cirrhosis of the liver: A controlled study. *Aust N Z J Med* 1977;7(6):596-9.
 510. Pusch H.H.. Oral treatment of oligozoospermia with testosterone-undecanoate: results of a double-blind-placebo-controlled trial. *Andrologia* 1989;21(5):76-82.
 511. Rabijewski M., M. Adamkiewicz, S. Zgliczynski. The influence of testosterone replacement therapy on well-being, bone mineral density and lipids in elderly men. *Polskie Archiwum Medycyny Wewnętrznej* 1998;100(3):212-21.
 512. Rabkin J.G., G. Wagner, R. Rabkin. Treatment of depression in HIV+ men: Literature review and report of an ongoing study of testosterone replacement therapy. *Ann Behav Med* 1996;18(1):24-9
 513. Rabkin J.G., G.J. Wagner, M.C. McElhiney, R. Rabkin, S.H. Lin. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. *J Clin Psychopharmacol* 2004;24(4):379-85.
 514. Rabkin J.G., G.J. Wagner, R. Rabkin. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry* 2000;57(2):141-7.
 515. Rabkin J.G., G.J. Wagner, R. Rabkin. Testosterone therapy for human immunodeficiency virus-positive men with and without hypogonadism. *J Clin Psychopharmacol* 1999; 19(1):19-27.
 516. Rabkin J.G., R. Rabkin, G. Wagner. Testosterone replacement therapy in HIV illness. *Gen Hosp Psychiatry* 1995;17(1):37-42.
 517. Ragnarsson O., M.G. Burt, K.K. Ho, G. Johannsson. Effect of short-term GH and testosterone administration on body composition and glucose homeostasis in men receiving chronic glucocorticoid therapy. *Eur J Endocrinol* 2013;168(2):243-51.
 518. Rajmil, M. Puig-Domingo, F. Tortosa, M. Viader, Patterson A. Garcia, D. Schwarzstein, Leiva A. de. Melatonin concentration before and during testosterone replacement in primary hypogonadic men. *Eur J Endocrinol* 1997;137(1):48-52.
 519. Rakic Z., V. Starcevic, V.P. Starcevic, J. Marinkovic. Testosterone treatment in men with erectile disorder and low levels of total testosterone in serum. *Arch Sex Behav* 1997;26(5):495-504.
 520. Raynaud J.P., C. Aumonier, V. Gualano, D. Betea, A. Beckers. Pharmacokinetic study of a new testosterone-in-adhesive matrix patch applied every 2 days to hypogonadal men. *J Steroid Biochem Mol Biol*. 2008;109(1-2):177-84.
 521. Reddy P., C.M. White, A.B. Dunn, N.M. Moyna, P.D. Thompson. The effect of testosterone on health-related quality of life in elderly males - a pilot study. *J Clin Pharm Ther* 2000;25(6):421-6.
 522. Ren X.M., J. Ying, D.H. Yao, Y.Q. Jiang, M.X. Xu. Pre- and post-prostatectomy variation and supplement of sexual hormones in patients with benign prostatic hyperplasia. *Zhonghua Nan Ke Xue* 2005;11:50.
 523. Reyes-Vallejo L., S. Lazarou, A. Morgentaler. Subjective sexual response to testosterone replacement therapy based on initial serum levels of total testosterone. *J Sex Med* 2007;4(6):1757-62.
 524. Rhoden E.L., A. Morgentaler. Symptomatic response rates to testosterone therapy and the likelihood of completing 12 months of therapy in clinical practice. *J Sex Med* 2010;7(1 pt 1):277-83.
 525. Rhoden E.L., A. Morgentaler. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: Results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003;170(6I):2348-51.
 526. Ribeiro R.S., J. Abucham. Recovery of persistent hypogonadism by clomiphene in males with prolactinomas under dopamine agonist treatment. *Eur J Endocrinol* 2009;161(1):163-9.

527. Richardson D., D. Goldmeier, G. Frize, H. Lamba, Souza C. De, A. Kocsis, G. Scullard. Letrozole versus testosterone. a single-center pilot study of HIV-infected men who have sex with men on highly active anti-retroviral therapy (HAART) with hypoactive sexual desire disorder and raised estradiol levels. *J Sex Med* 2007;4(2):502-8.
528. Rio G. Del, C. Carani, A. Velardo, G. Zizzo, M. Procopio, F. Coletta, P. Marrama, E. Ghigo. Effect of testosterone replacement therapy on the somatotrope responsiveness to GHRH alone or combined with pyridostigmine and on sympathoadrenal activity in patients with hypogonadism. *J Endocrinol Invest* 1995;18(9):690-5.
529. Rochira V., A. Balestrieri, B. Madeo, A.R. Granata, C. Carani. Sildenafil improves sleep-related erections in hypogonadal men: evidence from a randomized, placebo-controlled, crossover study of a synergic role for both testosterone and sildenafil on penile erections. *J Androl* 2006;27(2):165-75.
530. Rodriguez-Tolra J., J. Torremade, Gregorio S. di, Rio L. del, E. Franco. Effects of testosterone treatment on bone mineral density in men with testosterone deficiency syndrome. *Andrology* 2013;1(4):570-5.
531. Rohleder N., B.M. Kudielka, D.H. Hellhammer, J.M. Wolf, C. Kirschbaum. Age and sex steroid-related changes in glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress. *J Neuroimmunol* 2002;126(1-2):69-77.
532. Rolf C., Eckardstein S. von, U. Koken, E. Nieschlag. Testosterone substitution of hypogonadal men prevents the age-dependent increases in body mass index, body fat and leptin seen in healthy ageing men: Results of a cross-sectional study. *Eur J Endocrinol* 2002;146(4):505-11.
533. Rolf C., S. Kemper, G. Lemnitz, U. Eickenberg, E. Nieschlag. Pharmacokinetics of a new transdermal testosterone gel in gonadotrophin-suppressed normal men. *Eur J Endocrinol* 2002; 146(5):673-9.
534. Romano M. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. A randomized, double-blind, placebo-controlled study. *Ital Heart J* 2001; (Suppl 2):203.
535. Ronde W. de, Haan A. de, M.L. Drent. Quality of life is reduced in patients with Klinefelter syndrome on androgen replacement therapy. *Eur J Endocrinol* 2009;160(3):465-8.
536. Rosa M. De, L. Paesano, V. Nuzzo, S. Zarrilli, A. Del Puente, P. Oriente, G. Lupoli. Bone mineral density and bone markers in hypogonadotropic and hypergonadotropic hypogonadal men after prolonged testosterone treatment. *J Endocrinol Invest* 2001;24(4):246-52.
537. Rosano G.M., F. Leonardo, P. Pagnotta, F. Pelliccia, G. Panina, E. Cerquetani, P.L. della Monica, B. Bonfigli, M. Volpe, S.L. Chierchia. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*. 1999;99(13):1666-70.
538. Rose A.F., F. Gallo, M. Giglio, G. Carmignani. Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. *Urol* 2004;63(1):13-6.
539. Rosen R.C., F.C. Wu, H.M. Behre, C.G. Roehrborn, F.H. Schroder, F.S. Siami, J.F. Martha, J.D. Finn, A.B. Araujo. Registry of Hypogonadism in Men (RHYME): design of a multi-national longitudinal, observational registry of exogenous testosterone use in hypogonadal men. *Aging Male* 2013;16(1):1-7.
540. Rosenthal B.D., N.R. May, M.J. Metro, R.C. Harkaway, P.C. Ginsberg. Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. *Urology* 2006;67(3):571-4.
541. Ross R.J.M., A. Jabbar, T.H. Jones, B. Roberts, K. Dunkley, J. Hall, A. Long, H. Levine, D.R. Cullen. Pharmacokinetics and tolerability of a bioadhesive buccal testosterone tablet in hypogonadal men. *Eur J Endocrinol* 2004;150 (1):57-63.
542. Rota, M.C. Savanelli, L. Tauchmanova, S. Savastano, G. Lombardi, A. Colao, Somma C. Bone density and turnover in young adult patients with growth hormone deficiency after 2-year growth hormone replacement according with gender. *J Endocrinol Invest* 2008;31(2):94-102.
543. Rozhivanov R.V., D.G. Kurbatov. Sexual function rehabilitation of men with pituitary tumors. *Urologiia* 2010;48,50.
544. Rubinow K.B., T. Vaisar, C. Tang, A.M. Matsumoto, J.W. Heinecke, S.T. Page. Testosterone replacement in hypogonadal men alters the HDL proteome but not HDL cholesterol efflux capacity. *J Lipid Res* 2012;53(7):1376-83.
545. Ruiz E., E. Ortega, E. Sanchez-Cantalejo, C. Osorio. Effects of depot testosterone administration on serum levels of testosterone, FSH, LH and prolactin. *J Endocrinol Invest* 1980;3(4):385-8.
546. Ruvalcaba R.H.. Testosterone therapy in Klinefelter's syndrome (a prolonged observation). *Andrologia* 1989;21(6):535-41.
547. Saad F., L. Gooren, A. Haider, A. Yassin. An exploratory study of the effects of 12 month administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome. *Arch Androl* 2007;53(6):353-7.
548. Saad F., L. Gooren, A. Haider, A. Yassin. Effects of testosterone gel followed by parenteral testosterone undecanoate on sexual dysfunction and on features of the metabolic syndrome. *Andrologia* 2008;40(1):44-8.
549. Saad F.. Re: Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Eur Urol* 2012;62:932.
550. Sader M.A., K.A. Griffiths, M.R. Skilton, S.M. Wishart, D.J. Handelsman, D.S. Celmajer. Physiological testosterone replacement and arterial endothelial function in men. *Clin Endocrinol* 2003;59(1):62-7.

551. Sadovsky R., S. Dhindsa, K. Margo. Testosterone deficiency: which patients should you screen and treat? *J Fam Pract* 2007;56(5 suppl):S1-20.
552. Sai-zhu W., W. Zin-shi, Y. Xue. Antianginal and lipid lowering effects of oral androgenic preparation (andriol) on elderly male patients with coronary heart disease. *Chinese Journal of Internal Medicine* 1993;32:235.
553. Salamano G., G.C. Isaia, F. Pecchio, S. Appendino, M. Mussetta, G.M. Molinatti. Administration of testosterone to hypogonadic male: effects on calcium and phosphate metabolism. *Archivio Italiano di Urologia Nefrologia Andrologia* 1990;62(1):149-53.
554. Salehian B., C. Wang, G. Alexander, T. Davidson, V. McDonald, N. Berman, R.E. Dudley, F. Ziel, R.S. Swerdloff. Pharmacokinetics, bioefficacy, and safety of sublingual testosterone cyclodextrin in hypogonadal men: comparison to testosterone enanthate — a clinical research center study. *J Clin Endocrinol Metab* 1995;80(12):3567-75.
555. Salmimies P., G. Kockott, K.M. Pirke, H.J. Vogt, W.B. Schill. Effects of testosterone replacement on sexual behavior in hypogonadal men. *Arch Sex Behav* 1982;11(4):345-53.
556. Samaras N., D. Samaras, A. Chambellan, C. Pichard, R. Thibault. Pulmonary rehabilitation: the reference therapy for undernourished patients with chronic obstructive pulmonary disease. *Biomed Res Int*. 2014;2014:248420
557. Samtsova A.V. Influence of testosterone propionate on conditioned and unconditioned reflexes in men 59 to 72 years old. *Problemy Endokrinologii* 1957;2:6-11.
558. Sandner F.. Male hypogonadism needs a testosterone replacement. *Journal fur Pharmakologie und Therapie* 2010;19(2):58-9.
559. Sante S. di, W.P. Connors, A. Morgentaler. Influence of baseline serum testosterone on changes in body composition in response to testosterone therapy. *J Sex Med* 2012;9(2):585-93.
560. Santosa S., S. Khosla, L.K. McCready, M.D. Jensen. Effects of estrogen and testosterone on resting energy expenditure in older men. *Obesity (Silver Spring)* 2010;18(12):2392-4.
561. Sardar P., A. Jha, D. Roy, U. Majumdar, P. Guha, S. Roy, R. Banerjee, A.K. Banerjee, D. Bandyopadhyay. Therapeutic effects of nandrolone and testosterone in adult male HIV patients with AIDS wasting syndrome (AWS): a randomized, double-blind, placebo-controlled trial. *HIV Clin Trials* 2010;11(4):220-9.
562. Sarosdy M.F.. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007;109(3):536-41.
563. Sartorius G., C. Fennell, S. Spasevska, L. Turner, A.J. Conway, D.J. Handelsman. Factors influencing time course of pain after depot oil intramuscular injection of testosterone undecanoate. *Asian J Androl* 2010;12(2):227-33.
564. Sattler F.R., C. Castaneda-Sceppa, E.F. Binder, E.T. Schroeder, Y. Wang, S. Bhasin, M. Kawakubo, Y. Stewart, K.E. Yarasheski, J. Ullor, P. Colletti, R. Roubenoff, S.P. Azen. Testosterone and growth hormone improve body composition and muscle performance in older men. *J Clin Endocrinol Metab* 2009;94(6):1991-2001.
565. Sattler F.R., S. Bhasin, J. He, K.E. Yarasheski, E.F. Binder, E.T. Schroeder, C. Castaneda-Sceppa, M. Kawakubo, R. Roubenoff, M. Dunn, C. Hahn, Y. Stewart, C. Martinez, S.P. Azen. Durability of the effects of testosterone and growth hormone supplementation in older community-dwelling men: the HORMA Trial. *Clinical Endocrinology*. 2011;75:103
566. Sattler, S. Bhasin, J. He, C.P. Chou, C. Castaneda-Sceppa, K. Yarasheski, E. Binder, E.T. Schroeder, M. Kawakubo, A. Zhang, R. Roubenoff, S. Azen. Testosterone threshold levels and lean tissue mass targets needed to enhance skeletal muscle strength and function: the HORMA trial. *J Gerontology A Biol Sci Med Sci* 2011;66(1):122-9.
567. Saxton J.M., I. Zwierska, A. Mathur, K.S. Channer. Study protocol to investigate the effects of testosterone therapy as an adjunct to exercise rehabilitation in hypogonadal males with chronic heart failure. *BMC Cardiovasc Disord* 2006;6:46.
568. Schiavi R.C., D. White, J. Mandeli, A.C. Levine. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. *Arch Sex Behav* 1997;26(3):231-41.
569. Schoenfeld M.J., E. Shortridge, Z. Cui, D. Muram. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims analysis. *J Sex Med* 2013;10(5):1401-9.
570. Schooling C.M. Androgen activity, ischaemic heart disease and risk factors among men in NHANES III. *European Journal of Clinical Investigation*. 2013;43(12):1273
571. Schrader S., A. Mills, M. Schepeler, J.E. Block. Improvement in sexual functioning and satisfaction in nonresponders to testosterone gel: clinical effectiveness in hypogonadal, HIV-positive males. *Clin Cornerstone* 2005;7 Suppl 4:S26-31.
572. Schroeder E.T., C. Castaneda-Sceppa, Y. Wang, E.F. Binder, M. Kawakubo, Y. Stewart, T. Storer, R. Roubenoff, S. Bhasin, K.E. Yarasheski, F.R. Sattler, S.P. Azen. Hormonal regulators of muscle and metabolism in aging (HORMA): design and conduct of a complex, double masked multicenter trial. *Clin Trials* 2007; 4(5):560-71.
573. Schroeder E.T., J. He, K.E. Yarasheski, E.F. Binder, C. Castaneda-Sceppa, S. Bhasin, C.M. Dieli-Conwright, M. Kawakubo, R. Roubenoff, S.P. Azen, F.R. Sattler. Value of measuring muscle performance to assess changes in lean mass with testosterone and growth hormone supplementation. *Eur J Appl Physiol* 2012;112(3):1123-31.
574. Schultheiss D., D.M. Hiltl, M.R. Meschi, S.A. Machtens, M.C. Truss, C.G. Stief, U. Jonas. Pilot study of the transdermal application of testosterone gel to the penile skin for the treatment of hypogonadotropic men with erectile dysfunction. *World J Urol* 2000;18(6):431-5.

575. Schwab J., H.E. Kulin, E.J. Susman, J.W. Finkelstein, V.M. Chinchilli, S.J. Kunselman, L.S. Liben, M.R. D'Arcangelo, L.M. Demers. The role of sex hormone replacement therapy on self-perceived competence in adolescents with delayed puberty. *Child Dev* 2001;72(5):1439-50.
576. Schwarz E.R., R.D. Willix. Impact of a physician-supervised exercise-nutrition program with testosterone substitution in partial androgen-deficient middle-aged obese men. *J Geriatr Cardiol*. 2011;8(4):201-6
577. Scott J.D., P.R. Wolfe, P. Anderson, G.R. Cohan, A. Scarsella. Prospective study of topical testosterone gel (AndroGel) versus intramuscular testosterone in testosterone-deficient HIV-infected men. *HIV Clin Trials* 2007;8(6):412-20.
578. Seftel A. Re: Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: A parallel, randomized trial. *J Urol* 2013;190(1):208.
579. Seftel A. Re: effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blind placebo-controlled moscow study. *J Urology* 2011;185(2):635.
580. Seftel A. Re: Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Urol* 2013;190(3):988.
581. Seftel A.D. Low testosterone concentrations and the symptoms of testosterone deficiency according to the androgen deficiency in ageing males (ADAM) and ageing males' symptoms rating scale (AMS) questionnaires. *J Urol* 2011;185(5):1835.
582. Seftel A.D. Re: A small-scale clinical trial to determine the safety and efficacy of testosterone replacement therapy in hypogonadal men with spinal cord injury. *J Urol* 2012;187(2):558.
583. Seftel A.D. Re: A. Aversa, R. Bruzziches, D. Francomano, G. Rosano, A.M. Isidori, A. Lenzi, G. Spera. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 24-month, randomized, double-blind, placebo-controlled study. *J Urol* 2011;185(2):634.
584. Seftel A.D. Re: Effect of testosterone supplementation with and without a dual 5alpha-reductase inhibitor on fat-free mass in men with suppressed testosterone production: A randomized controlled trial. *J Urol* 2012;188:906
585. Seftel A.D. Re: IPASS: A study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. *J Urol* 2013;189(1):250-1.
586. Seftel A.D. Re: Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: A randomized, placebo-controlled clinical trial. *J Urology* 2012;187(1):235-6.
587. Seftel A.D. Re: testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *J Urol* 2014;191(3): 750-1.
588. Seftel A.D. Testosterone Treatment Improves Body Composition and Sexual Function in Men With COPD, in a 6-Month Randomized Controlled Trial. *J Urol* 2005;173:1278.
589. Seidman S.N., E. Spatz, C. Rizzo, S.P. Roose. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry* 2001;62(6):406-12.
590. Seidman S.N., G. Orr, G. Raviv, R. Levi, S.P. Roose, E. Kravitz, R. Amiaz, M. Weiser. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. *J Clin Psychopharmacol* 2009;29(3):216-21.
591. Seidman S.N., J.G. Rabkin. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord* 1998;48(2-3):157-61.
592. Seidman S.N., M. Miyazaki, S.P. Roose. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: randomized placebo-controlled clinical trial. *J Clin Psychopharmacol* 2005;25(6):584-8.
593. Seidman S.N., S.P. Roose. The sexual effects of testosterone replacement in depressed men: randomized, placebo-controlled clinical trial. *J Sex Marital Ther* 2006; 32(3):267-73.
594. Selice R., N. Caretta, Mambro A. Di, M. Torino, P. Palego, A. Ferlin, C. Foresta. Prostate volume and growth during testosterone replacement therapy is related to visceral obesity in Klinefelter syndrome. *Eur J Endocrinol* 2013;169(6):743-9.
595. Seth M., A. Sachdeva, P. Saharoy, S. Seth, H. Madaan. Relationship of testosterone levels in males with coronary heart disease. *Int J Pharma Bio Sciences* 2011;2(2):566-70.
596. Shabsigh A., Y. Kang, R. Shabsigh, M. Gonzalez, G. Liberson, H. Fisch, E. Goluboff. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. *J Sex Med* 2005;2(5):716-21.
597. Shabsigh R., J.M. Kaufman, C. Steidle, H. Padma-Nathan. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172(2):658-63.
598. Shabsigh R.. Testosterone therapy in erectile dysfunction. *Aging Male* 2004;7(4):312-8.
599. Shah K., C. Montoya, R.K. Persons. Clinical inquiries. Do testosterone injections increase libido for elderly hypogonadal patients? *J Fam Pract* 2007;56(4):301-3.
600. Shahbazian H.B., K. Molaw, A. Zarea, M. Zakerkish, A.M. Aleali. Effect of various drug treatments on bone density in hypogonadal men. *Pakistan J Med Sci* 2012;28(4).

601. Shamloul R., H. Ghanem, I. Fahmy, A. El-Meleigy, S. Ashoor, A. Elnashaar, I. Kamel. Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. *J Sex Med* 2005;2(4):559.
602. Shaughnessy A.F.. Testosterone does not improve sildenafil effectiveness. *Am Fam Phys* 2013;88(5):333-4.
603. Sheffer A.L., D.T. Fearon, K.F. Austen. Methyltestosterone therapy in hereditary angioedema. *Ann Intern Med* 1977;86(3):306-8.
604. Shi Y.F. Effect of long-term testosterone therapy on the masculinization of hypogonadal men. *Chung Hua I Hsueh Tsa Chih* 1989;69:582.
605. Shimon I., A. Lubina, M. Gorfine, J. Ilany. Feedback inhibition of gonadotropins by testosterone in men with hypogonadotropic hypogonadism: Comparison to the intact pituitary-testicular axis in primary hypogonadism. *J Androl* 2006;27(3):358-64.
606. Shores M.M., K.L. Sloan, A.M. Matsumoto, V.M. Moceri, B. Felker, D.R. Kivlahan. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry* 2004;61(2):162-7.
607. Shu D.-F., B.-R. Dong. A randomized controlled trial of testosterone undecanoate for improving quality of life of the elderly male patients with chronic disease in advanced stage. *Chinese Journal of Evidence-Based Medicine* 2005;5(8):599-604.
608. Sicotte N.L., B.S. Giesser, V. Tandon, R. Klutch, B. Steiner, A.E. Drain, D.W. Shattuck, L. Hull, H.J. Wang, R.M. Elashoff, R.S. Swerdloff, R.R. Voskuhl. Testosterone treatment in multiple sclerosis: a pilot study. *Arch Neurol* 2007;64(5):683-8.
609. Siegel J.A., L.A. Young, M.B. Neiss, M.H. Samuels, C.E. Roselli, J.S. Janowsky. Estrogen, testosterone, and sequential movement in men. *Behav Neurosci* 2008;122(5):955-62.
610. Simon D., M.A. Charles, K. Nahoul, G. Orssaud, J. Kremiski, V. Hully, E. Joubert, L. Papoz, E. Eschwege. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. *J Clin Endocrinol Metab* 1997;82(2):682-5.
611. Singh A.B., K. Norris, N. Modi, I. Sinha-Hikim, R. Shen, T. Davidson, S. Bhasin. Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab* 2001;86(6):2437-45.
612. Sisci, S. Aquila, A. Carpino, M.T. Sessa, E. Beraldi, M. Buffone, S. Ando. Response of adnexal glands to short treatment with high doses of testosterone undecanoate/mesterolone in adult men. *Advan Contracep Deliver Sys* 1993;9(4):239-47.
613. Skakkebaek N.E., J. Bancroft, D.W. Davidson, P. Warner. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol* 1981;14(1):49-61.
614. Slob A.K., van der Werff ten Bosch JJ, E.V. van Hall, F.H. de Jong, W.C. Weijmar Schultz, F.A. Eikelboom. Psychosexual functioning in women with complete testicular feminization: is androgen replacement therapy preferable to estrogen? *J Sex Marital Ther* 1993;19(3):201-9.
615. Smith A.M., K.M. English, C.J. Malkin, R.D. Jones, T.H. Jones, K.S. Channer. Testosterone does not adversely affect fibrinogen or tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) levels in 46 men with chronic stable angina. *Eur J Endocrinol* 2005;152(2):285-91.
616. Snyder P.J., H. Peachey, J.A. Berlin, D. Rader, D. Usher, L. Loh, P. Hannoush, A. Dlewati, J.H. Holmes, J. Santanna, B.L. Strom. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *Am J Med* 2001;111(4):255-60.
617. Snyder P.J., H. Peachey, P. Hannoush, J.A. Berlin, L. Loh, D.A. Lenrow, J.H. Holmes, A. Dlewati, J. Santanna, C.J. Rosen, B.L. Strom. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(4):2647-53.
618. Snyder P.J., H. Peachey, P. Hannoush, J.A. Berlin, L. Loh, J.H. Holmes, A. Dlewati, J. Staley, J. Santanna, S.C. Kapoor, M.F. Attie, J.G. Haddad, B.L. Strom. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(6):1966-72.
619. Sofikitis N.. High androgen dose treatment in men with chronic renal failure (CRF) improves fertility prognosis after kidney transplantation (KTR). *Fertil Steril* 1992; 58:S24.
620. Sokol R.Z., A. Palacios, L.A. Campfield, C. Saul, R.S. Swerdloff. Comparison of the kinetics of injectable testosterone in eugonadal and hypogonadal men. *Fertil Steril* 1982;37(3):425-30.
621. Sokolnicki L.A., S. Khosla, N. Charkoudian. Effects of testosterone and estradiol on cutaneous vasodilation during local warming in older men. *Am J Physiol Endocrinol Metab* 2007;293(5):E1426-9.
622. Solomon L.R., E.D. Hendler. Androgen therapy in haemodialysis patients: further observations on erythropoiesis and ferrokinetics. *Br J Haematol* 1988;69(3):426-7.
623. Song, Z.-M. Cai. Effectiveness of testosterone undecanoate treatment in men with asthenospermia. *Journal of Reproduction and Contraception*.2012;23(2):119-26
624. Sonmez A., C. Haymana, E. Bolu, A. Aydogdu, S. Tapan, M. Serdar, B. Altun, C. Barcin, A. Taslipinar, C. Meric, G. Uckaya, M. Kutlu. Metabolic syndrome and the effect of testosterone treatment in young men with congenital hypogonadotropic hypogonadism. *Eur J Endocrinol* 2011;164(5):759-64.
625. Span J.P.T., G.F.F.M. Pieters, C.G.J. Sweep, A.R.M.M. Hermus, A.G.H. Smals. Gender difference in insulin-like growth factor I response to growth hormone (GH) treatment in GH-deficient adults: Role of sex hormone replacement. *J Clin Endocrinol Metab* 2000;85(3):1121-5.

626. Srinivasan M, Irving BA, Frye RL, et al. Effects on lipoprotein particles of long-term dehydroepiandrosterone in elderly men and women and testosterone in elderly men. *J Clin Endocrinol Metab* 2010;95:1617.
627. Steidle C., M.A. Witt, J. Matrisciano, J.E. Block. Sexual functioning and satisfaction in nonresponders to testosterone gel: potential effectiveness of retreatment in hypogonadal males. *Clin Cornerstone* 2005;7 Suppl 4:S20-5.
628. Stenn P.G., E.L. Klaiber, W. Vogel, D.M. Broverman. Testosterone effects upon photic stimulation of the electroencephalogram (EEG) and mental performance of humans. *Percept mot skills* 1972; 34(2):371-8.
629. Stief J., H.Y. Sohn, A. Alt, P. Uberfuhr, K. Theisen, H.U. Stempfle. Effect of immunosuppression-induced hypogonadism on bone metabolism after heart transplantation. *Deutsche Medizinische Wochenschrift* 2004;129:1674.
630. Stillman M.J. Testosterone replacement therapy for treatment refractory cluster headache. *Headache* 2006;46(6):925-33.
631. Storer T.W., L. Woodhouse, L. Magliano, A.B. Singh, C. Dzekov, J. Dzekov, S. Bhasin. Changes in muscle mass, muscle strength, and power but not physical function are related to testosterone dose in healthy older men. *J Am Geriatr Soc* 2008;56(11):1991-9.
632. Summers V.K.. Treatment of angina of effort with androgens. *Lancet* 1948;1(14):519.
633. Sun P., A. Seftel, R. Swindle, W. Ye, G. Pohl. The costs of caring for erectile dysfunction in a managed care setting: evidence from a large national claims database. *J Urol* 2005;174(5):1948-52.
634. Svartberg J., U. Aasebo, A. Hjalmsen, J. Sundsfjord, R. Jorde. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Respir Med* 2004;98(9):906-13.
635. Svartberg, U. Aasebo, A. Hjalmsen, J. Sundsfjord, R. Jorde. Testosterone treatment increases fat free mass, reduces fat mass and improves sexual function in men with COPD, in a 6 month randomised controlled trial [Abstract]. *Eur Respir J* 2003;22.
636. Svetec D.A., E.D. Canby, I.M. Thompson, E.S. Sabanegh. The effect of parenteral testosterone replacement on prostate specific antigen in hypogonadal men with erectile dysfunction. *J Urol* 1997;158(5):1775-7.
637. Swyer G.I. Effects of testosterone implants in men with defective spermatogenesis. *Br Med J* 1953;2(4845):1080-1.
638. Szmulewitz R., S. Mohile, E. Posadas, R. Kunnavakkam, T. Karrison, E. Manchen, W.M. Stadler. A randomized phase I study of testosterone replacement for patients with low-risk castration-resistant prostate cancer. *Eur Urol* 2009;56(1):97-103.
639. Szmulewitz R.Z., E.M. Posadas, B. Manchen, W.M. Stadler. A randomized, double-blind, placebo-controlled phase II study of testosterone replacement in men with asymptomatic castrate-resistant prostate cancer (PC) [Abstract TPS241]. *J Clin Oncology* 2010;28:41.
640. Takao T., A. Tsujimura, J. Nakayama, Y. Matsuoka, Y. Miyagawa, S. Takada, N. Nonomura, A. Okuyama. Lower urinary tract symptoms after hormone replacement therapy in Japanese patients with late-onset hypogonadism: A preliminary report. *Int J Urol* 2009;16(2):212-4.
641. Taniguchi H., G. Kawa, H. Kinoshita, T. Matsuda. Symptomatic change in Japanese hypogonadal patients several years after androgen replacement therapy. *Aging Male* 2011;14(3):190-4.
642. Tariq S.H., U. Haleem, M.L. Omran, F.E. Kaiser, H.M. Perry, J.E. Morley. Erectile dysfunction: etiology and treatment in young and old patients. *Clin Geriatr Med* 2003;19(3):539-51.
643. Testosterone gel associated with increased risk of cardiovascular events. *Aust J Phar* 2011;92 (1092):84.
644. Testosterone gel shows promise in Phase III trial. *AIDS Alert* 1999;14(6):67.
645. Testosterone in the treatment of arterial insufficiency of the lower limbs. *Scand J Clin Lab Invest* 1967;19:482-8.
646. Testosterone replacement therapy has no harmful effect on prostate tissue. *Nat Clin Prac Endocrinol Metab* 2007;3(3):201-2.
647. Testosterone therapy may be beneficial for men with late-onset depression. *Brown University Geriatr Psychopharmacol Update* 2003;7:3
648. Testosterone topical solution (Axiron) for hypogonadism. *Med Lett Drugs Ther* 2011;53(1368):54-5.
649. Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. The Copenhagen Study Group for Liver Diseases. *Hepatology* 1986;6(5):807-13.
650. Thompson P.D., A.W. Ahlberg, N.M. Moyna, B. Duncan, M. Ferraro-Borgida, C.M. White, C.C. McGill, G.V. Heller. Effect of intravenous testosterone on myocardial ischemia in men with coronary artery disease. *Am Heart J* 2002;143(2):249-56.
651. Thomsen H.H., H.J. Moller, C. Trolle, K.A. Groth, A. Skakkebaek, A. Bojesen, C. Host, C.H. Gravholt. The macrophage low-grade inflammation marker sCD163 is modulated by exogenous sex steroids. *Endocr.* 2013;2(4):216-24.
652. Tirabassi G., Muti N. Delli, A. Gioia, A. Biagioli, A. Lenzi, G. Balercia. Effects of testosterone replacement therapy on bone metabolism in male post-surgical hypogonadotropic hypogonadism: Focus on the role of androgen receptor CAG polymorphism. *J Endocrinol Invest* 2014; 37(4):393-400.
653. Tirabassi G., Muti N. Delli, G. Corona, M. Maggi, G. Balercia. Androgen receptor gene CAG repeat polymorphism regulates the metabolic effects of testosterone replacement therapy in male postsurgical hypogonadotropic hypogonadism. *Int J Endocrinol* 2013;2013:816740.

654. Traish A.M., A. Haider, G. Doros, F. Saad. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: An observational, long-term registry study. *Int J Clin Pract* 2014;68(3):314-29.
655. Tripathy D., P. Shah, R. Lakshmy, K.S. Reddy. Effect of testosterone replacement on whole body glucose utilisation and other cardiovascular risk factors in males with idiopathic hypogonadotrophic hypogonadism. *Horm Metab Res* 1998;30(10):642-5.
656. Tschop M., H.M. Behre, E. Nieschlag, R.A. Dressendorfer, C.J. Strasburger. A time-resolved fluorescence immunoassay for the measurement of testosterone in saliva: monitoring of testosterone replacement therapy with testosterone buciclate. *Clin Chem Lab Med* 1998;36(4):223-30.
657. Ulas U.H., E. Bolu, Y. Kutukcu, E. Unlu, M. Ozata, O. Oz, Z. Odabasi. The effect of testosterone therapy on event related potentials in male idiopathic hypogonadotropic hypogonadism. *Neurol Psychiatry Brain Res* 2007;14(1):25-30.
658. Uyanik B.S., Z. Ari, B. Gumus, M.R. Yigitoglu, T. Arslan. Beneficial effects of testosterone undecanoate on the lipoprotein profiles in healthy elderly men. A placebo controlled study. *Jp Heart J* 1997;38(1):73-82.
659. Vague J., J. Nicolino, J.C. Pouch. Effects of testosterone on the adipo-muscular ratio in eunuchoid males. *Annales d'Endocrinologie* 1968;29:370.
660. Veldhuis J.D., C.Y. Bowers. Determinants of GH-releasing hormone and GH-releasing peptide synergy in men. *Am J Physiol Endocrinol Metab* 2009;296(5):E1085-92.
661. Veldhuis J.D., D. Erickson, J. Wigham, S. Weist, J.M. Miles, C.Y. Bowers. Gender, sex-steroid, and secretagogue-selective recovery from growth hormone-induced feedback in older women and men. *J Clin Endocrinol Metab* 2011;96(8):2540-7.
662. Veldhuis J.D., D.M. Keenan, J.N. Bailey, A. Adeniji, J.M. Miles, R. Paulo, M. Cosma, C. Soares-Welch. Testosterone supplementation in older men restrains insulin-like growth factor's dose-dependent feedback inhibition of pulsatile growth hormone secretion. *J Clin Endocrinol Metab* 2009;94(1):246-54.
663. Veldhuis J.D., D.M. Keenan, K. Mielke, J.M. Miles, C.Y. Bowers. Testosterone supplementation in healthy older men drives GH and IGF-I secretion without potentiating peptidyl secretagogue efficacy. *Eur J Endocrinol* 2005;153(4):577-86.
664. Vigna G.B., E. Bergami. Testosterone replacement, cardiovascular system and risk factors in the aging male. *J Endocrinol Invest* 2005;28(11):69-74.
665. Vorkas C.K., C.M. Vaamonde, M.J. Glesby. Testosterone replacement therapy and polycythemia in HIV-infected patients. *AIDS* 2012;26(2):243-5.
666. Wagner G., J. Rabkin, R. Rabkin. Effects of testosterone replacement therapy on sexual interest, function, and behavior in HIV+ men. *J Sex Res* 1997;34(1):27-33.
667. Wagner G.J., J.G. Rabkin, R. Rabkin. A randomized comparative trial of testosterone and protein supplements for weight loss in HIV+ men. *Nutrit Res* 2001;21(1-2):159-69.
668. Wagner G.J., J.G. Rabkin, R. Rabkin. Effects of testosterone on weight and body composition in men with human immunodeficiency virus-related weight loss. *Nutrit Res* 1999;19(2):227-233.
669. Wagner G.J., J.G. Rabkin, R. Rabkin. Testosterone as a treatment for fatigue in HIV+ men. *Gen Hosp Psychiatry* 1998;20(4):209-13.
670. Wang C., A. Iranmanesh, N. Berman, V. McDonald, B. Steiner, F. Ziel, S.M. Faulkner, R.E. Dudley, J.D. Veldhuis, R.S. Swerdloff. Comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone gel in healthy elderly men — a clinical research center study. *J Clin Endocrinol Metab* 1998;83(8):2749-57.
671. Wang C., C.W. Chan, K.K. Wong, K.K. Yeung. Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. *Fertil Steril* 1983;40(3):358-65.
672. Wang C., G. Alexander, N. Berman, B. Salehian, T. Davidson, V. McDonald, B. Steiner, L. Hull, C. Callegari, R.S. Swerdloff. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *J Clin Endocrinol Metab* 1996;81(10):3578-83.
673. Wang C., M. Harnett, A.S. Dobs, R.S. Swerdloff. Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. *J Androl* 2010;31(5):457-65.
674. Wang C., N. Berman, J.A. Longstreth, B. Chuapoco, L. Hull, B. Steiner, S. Faulkner, R.E. Dudley, R.S. Swerdloff. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. *J Clin Endocrinol Metab* 2000;85(3):964-9.
675. Wang H.-P., X. Liu, W.-J. Yan, R.-L. Zhao, Z.-Q. Cong. Therapeutic evaluation of testosterone propionate for cluster headache. *Chinese Journal of Clinical Rehabilitation* 2006;10(36):56-58.
676. Webb C.M., A.G. Elkington, M.M. Kraidly, N. Keenan, D.J. Pennell, P. Collins. Effects of oral testosterone treatment on myocardial perfusion and vascular function in men with low plasma testosterone and coronary heart disease. *Am J Cardiol* 2008;101(5):618-24.
677. Webb C.M., D.L. Adamson, Zeigler D. de, P. Collins. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol* 1999;83(3):437-9.

678. Wehkalampi K., K. Vangonen, T. Laine, L. Dunkel. Progressive reduction of relative height in childhood predicts adult stature below target height in boys with constitutional delay of growth and puberty. *Horm Res* 2007;68(2):99-104.
679. Welch B.J., M.A. Denke, A. Kermani, B. Adams-Huet, N.M. Gazmen, U. Gruntmanis. Comparison of testosterone, alendronate, and a combination of both therapies in men with low bone mineral density. *J Invest Med* 2007;55(4):168-73.
680. Welle S., R. Jozefowicz, G. Forbes, R.C. Griggs. Effect of testosterone on metabolic rate and body composition in normal men and men with muscular dystrophy. *J Clin Endocrinol Metab* 1992;74(2):332-5.
681. Wiehle R., G.R. Cunningham, N. Pitteloud, J. Wike, K. Hsu, G.K. Fontenot, M. Rosner, A. Dwyer, J. Podolski. Testosterone restoration using enclomiphene citrate in men with secondary hypogonadism: A pharmacodynamic and pharmacokinetic study. *BJU Int* 2013;112(8):1188-1200.
682. Wilson D.E., A.W. Meikle, S.C. Boike, A.J. Fairless, R.C. Etheredge, D.K. Jorkasky. Bioequivalence assessment of a single 5 mg/day testosterone transdermal system versus two 2.5 mg/day systems in hypogonadal men. *J Clin Pharmacol* 1998;38(1):54-9.
683. Wilson D.E., K. Kaidbey, S.C. Boike, D.K. Jorkasky. Use of topical corticosteroid pretreatment to reduce the incidence and severity of skin reactions associated with testosterone transdermal therapy. *Clin Ther* 1998;20(2):299-306.
684. Winters S.J., L. Atkinson. Serum LH concentrations in hypogonadal men during transdermal testosterone replacement through scrotal skin: further evidence that ageing enhances testosterone negative feedback. The Testoderm Study Group. *Clin Endocrinol* 1997;47(3):317-22.
685. Wittert G.A., I.M. Chapman, M.T. Haren, S. Mackintosh, P. Coates, J.E. Morley. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Ger A Biol Sci Med Sci* 2003;58(7):618-25.
686. Wong F.H., K.K. Pun, C. Wang. Loss of bone mass in patients with Klinefelter's syndrome despite sufficient testosterone replacement. *Osteoporosis Int* 1993;3(1):3-7.
687. Wright N.D., T. Edwards, S.M. Fleming, R.J. Dolan. Testosterone induces off-line perceptual learning. *Psychopharmacology* 2012;224(3):451-7.
688. Wu F.C., J. Bancroft, D.W. Davidson, K. Nicol. The behavioural effects of testosterone undecanoate in adult men with Klinefelter's syndrome: a controlled study. *Clin Endocrinol* 1982;16(5):489-97.
689. Wu F.C.W., G.M.H. Waites, T.M.M. Farley, A. Peregoudov. Effects of testosterone enanthate in normal men: Experience from a multicenter contraceptive efficacy study. *Fertil Steril* 1996;65:626.
690. Wu S., X. Weng. Regulation of atrial natriuretic peptide, thromboxane and prostaglandin production by androgen in elderly men with coronary heart disease. *Chin Med Sci J* 1993;8(4):207-9.
691. Wu S., X. Weng. Therapeutic effect of andriol on serum lipids and apolipoproteins in elderly male coronary heart disease patients. *Chin Med Sci J* 1992;7(3):137-41.
692. Wu S.Z., X.Z. Weng. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chin Med J* 1993;106(6):415-8.
693. Wu X., J. Mao, S. Lu, Z.-M. Jin, Y. Shi. The effect of androgen replacement therapy in hypogonadal young male patients on serum lipid profile and hsCRP level. *Chinese Journal of Andrology* 2007;21 (2):31-3.
694. Wylie K., D. Davies-South. A study of treatment choices in men with erectile dysfunction and reduced androgen levels. *J Sex Marital Ther* 2004;30:107-14.
695. Yamaguchi K., T. Ishikawa, K. Chiba, M. Fujisawa. Assessment of possible effects for testosterone replacement therapy in men with symptomatic late-onset hypogonadism. *Andrologia* 2011;43(1):52-6.
696. Yang L., S.X. Zhang, Q. Dong, Z.B. Xiong, X. Li. Application of hormonal treatment in hypogonadotropic hypogonadism: more than ten years experience. *Int Urol Nephrol* 2012;44(22):393-9.
697. Yang S.X., S.Z. Ji, W. Chen, D. Wang, K. Wang, H. Wang, A.P. Wang, G.W. Han, L.L. Liu, H.Z. Yang, X.J. Zhu. A double blind randomized placebo controlled clinical trial of finasteride in the treatment of androgenetic alopecia. *The Chinese Journal of Clinical Pharmacology* 2002;18:3.
698. Yap F., W. Hogler, J. Briody, B. Moore, R. Howman-Giles, C.T. Cowell. The skeletal phenotype of men with previous constitutional delay of puberty. *J Clin Endocrinol Metab* 2004;89(9):4306-11.
699. Yassin A.A., A. Haider, M. Zitzmann, D.-J. Yassin, P.G. Hammerer, F. Saad. Three cohorts' study in terms of incidence of prostate cancer in hypogonadal patients on long-term treatment with testosterone undecanoate injections. *Urologe — Ausgabe A*. 65.Kongresses der Deutschen Gesellschaft für Urologie Dresden Germany. 2013;52(1 Suppl 1):46-7.
700. Yassin A.A., F. Saad, H.E. Diede. Testosterone and erectile function in hypogonadal men unresponsive to tadalafil: results from an open-label uncontrolled study. *Andrologia* 2006;38(2):61-8.
701. Yassin A.A., F. Saad. Improvement of sexual function in men with late-onset hypogonadism treated with testosterone only. *J Sex Med* 2007;4(2):497-501.
702. Yassin A.A., F. Saad. Plasma levels of dihydrotestosterone remain in the normal range in men treated with long-acting parenteral testosterone undecanoate. *Andrologia* 2007;39(5):181-4.
703. Yassin D.J., A.A. Yassin, P.G. Hammerer. Combined testosterone and vardenafil treatment for restoring erectile function in hypogonadal patients who failed to respond to testosterone therapy alone. *J Sex Med* 2014;11(2):543-52.

704. Yates W.R., P.J. Perry, J. MacIndoe, T. Holman, V. Ellingrod. Psychosexual effects of three doses of testosterone cycling in normal men. *Biol Psychiatry* 1999;45(3):254-60.
705. Yesilova Z., M. Ozata, C. Oktenli, S.Y. Sanisoglu, M.K. Erbil, K. Dagalp. Effect of supraphysiologic doses of testosterone on fasting plasma total homocysteine concentrations in men with Klinefelter's syndrome. *Fertil Steril* 2004;81(5):1278-82.
706. Yin, E. Alfadhli, M. Htun, R. Dudley, S. Faulkner, L. Hull, A. Leung, R. Bross, J. Longstreth, R. Swerdloff, C. Wang. Dietary fat modulates the testosterone pharmacokinetics of a new self-emulsifying formulation of oral testosterone undecanoate in hypogonadal men. *Journal of Andrology*. 2012/11//. 33:1282
707. Young L.A., M.B. Neiss, M.H. Samuels, C.E. Roselli, J.S. Janowsky. Cognition is not modified by large but temporary changes in sex hormones in men. *J Clin Endocrinol Metab* 2010;95(1):280-8.
708. Yu Z., S.K. Gupta, S.S. Hwang, D.M. Cook, M.J. Duckett, L.E. Atkinson. Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol* 1997;37(12):1129-38.
709. Yu Z., S.K. Gupta, S.S. Hwang, M.S. Kipnes, A.D. Mooradian, P.J. Snyder, L.E. Atkinson. Testosterone pharmacokinetics after application of an investigational transdermal system in hypogonadal men. *J Clin Pharmacol* 1997;37(12):1139-45.
710. Yurci A., M. Yucesoy, K. Unluhizarci, E. Torun, S. Gursoy, M. Baskol, K. Guven, O. Ozbakir. Effects of testosterone gel treatment in hypogonadal men with liver cirrhosis. *Clin Res Hepatol Gastroenterol* 2011;35(12):845-54.
711. Zacharin M.R., J. Pua, S. Kanumakala. Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol* 2003;58(6):691-5.
712. Zainutdinova G.K., V.B. Mal'khanov. Use of testosterone preparations in complex therapy of severe herpetic keratitis in male patients. *Vestnik Oftalmologii* 2004;120:24.
713. Zajac A., M. Wilk, T. Socha, A. Maszczyk, J. Chycki. Effects of growth hormone and testosterone therapy on aerobic and anaerobic fitness, body composition and lipoprotein profile in middle-aged men. *Ann Agric Environ Med* 2014;21(1):156-60.
714. Zgliczynski S., Srzednicka J. Slowinska, A. Brezezinska, M. Ossowski, W. Zgliczynski. Beneficial effects of hormone replacement therapy: testosterone in hypogonadal men and estrogen in postmenopausal women on plasma IGF-I, lipids and lipoproteins concentrations. 8th International Congress on the Menopause. 1996;176.
715. Zgliczynski S., M. Ossowski, J. Slowinska-Srzednicka, A. Brzezinska, W. Zgliczynski, P. Soszynski, E. Chotkowska, M. Srzednicki, Z. Sadowski. Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis* 1996;121(1):35-43.
716. Zhang C., Y. Li, H. Zhao. Curative effect of Chinese drugs combined with Andriol in the treatment on 30 cases of late onset hypogonadism in males. *Chinese Journal of Andrology* 2007;21(6):46-7.
717. Zhang G.-Y., Y.-Q. Gu, X.-H. Wang, Y.-G. Cui, W.J. Bremner. A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. *J Androl* 1998;19(6):761-8.
718. Zhang W., P. Li, Z.K. Cai, J.H. Zheng, J.C. Dai, Y.X. Wang, Z. Wang, Z. Li. Safety and efficacy of L-carnitine and tadalafil for late-onset hypogonadism with ED: a randomized controlled multicenter clinical trial. *Zhonghua Nan Ke Xue* 2014;20:133.
719. Zhang X.H., X.S. Liu, B. Vasilic, F.W. Wehrli, M. Benito, C.S. Rajapakse, P.J. Snyder, X.E. Guo. In vivo muMRI-based finite element and morphological analyses of tibial trabecular bone in eugonadal and hypogonadal men before and after testosterone treatment. *J Bone Miner Res* 2008;23(9):1426-34.
720. Zhao W., H. Ye, X. Zhao, Z. Zhang, S. Sun, Y. Jiang, M. He, C. Xu, R. Hu, Y. Li. A network investigation on idiopathic hypogonadotropic hypogonadism in China. *Int J Endocrinol* 2013; 2013:591012.
721. Zheng X.F., P. Li. [Study on effects of acupuncture combined with medication on reproductive endocrines in the patient of PADAM]. *Zhongguo zhen jiu [Chinese acupuncture & moxibustion]* 2007;27:333.
722. Zhong J., G. Liang, P. Li, J. Dai, D. Xu, P. Ping, Z. Li. A multicenter research of sildenafil combined with testosterone undecanoate for treatment of erectile dysfunction with diabetes. *Chinese Journal of Andrology* 2013;27(4):26-29.
723. Zhou S.H., Z.W. Weng, T.L. Li. [The method of tonifying kidneys and activating blood circulation increases testosterone secretion index in late-onset hypogonadism males with kidney deficiency.] *Zhonghua Nan Ke Xue* 2013;19(7):647-51
724. Zhuravlev V.N., M.A. Frank, A.I. Gomzhin. Sexual functions of men with obstructive sleep apnoea syndrome and hypogonadism may improve upon testosterone administration: a pilot study. *Andrologia* 2009;41(3):193-5.
725. Zitzmann M., E. Nieschlag. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. *J Clin Endocrinol Metab* 2007;92(10):3844-53.
726. Zitzmann M., M. Brune, E. Nieschlag. Vascular reactivity in hypogonadal men is reduced by androgen substitution. *J Clin Endocrinol Metab* 2002;87(11):5030-7.

APPENDIX 4: LIST OF CONFERENCE ABSTRACTS

1. Abdullaev T, Mardanov BU, Kurbanov RD. Anabolic deficiency in dilated cardiomyopathy patients, and possibilities of replacement therapy with long- acting testosterone. *Heart Failure 2009 Nice France. Conference Start: 20090530 Conference End: 20090602. European Journal of Heart Failure* 2009;8:ii314.
2. Aggarwal B, Frankel J, Welliver C, et al. Testosterone pellets (testopela) insertion results in reversible suppression of pituitary gonadotropins (GT). *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:296.
3. Agustsson TT, McGowan B, Powrie J, et al. Polycythemia is common during any testosterone replacement and suppressed gonadotropin may predict polycythemia in primary hypogonadism. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews* 2011;32(3 Meeting Abstracts).
4. Ahern T, Khattak A, Reece R, et al. Effects of normalising testosterone and oestradiol levels on cardiovascular and bone health in men with severe obesity: A randomised clinical trial. *38th Annual Meeting of the Irish Endocrine Society Kilkenny Ireland. Conference Start: 20131108 Conference End: 20131109. Irish Journal of Medical Science* 2013; 182:S401-S402
5. Alavian M, Rotker K, Nelson B, et al. Effect of subcutaneous testosterone pellet therapy on developing secondary polycythemia. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology* 2014;191(4 Suppl 1):e529.
6. Amiaz R, Pope H, Seidman SN, et al. Testosterone gel replacement improves sexual function in hypogonadal depressed men taking antidepressants. *23rd European College of Neuropsychopharmacology, ECNP Congress Amsterdam Netherlands. Conference Start: 20100828 Conference End: 20100901. European Neuropsychopharmacology* 2010;20:S374.
7. Anderson K, Church A, Bradic C, et al. Effects of testosterone replacement on cognition in men with low testosterone levels and mild cognitive impairment. *Alzheimer's Association International Conference 2012 Vancouver, BC Canada. Conference Start: 20120714 Conference End: 20120719. Alzheimer's and Dementia* 2012;8(4 Suppl 1):P364
8. Andreadakis S, Konstantinidis C, Kartsaklis P, et al. The role of hypogonadism in no response to PDE-5 inhibitors and the impact of the use of testosterone gel in the treatment of ED. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine.* 2009;6:82
9. Aversa A, Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 36-month controlled study. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:403.
10. Aversa A, Bruzziches R, Francomano D, et al. Efficacy and safety of different testosterone undecanoate preparations in men with hypogonadism: A single-blind, randomized, placebo-controlled, 12-month follow-up study. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine* 2009;6:79.
11. Aversa A, Francomano D, Bruzziches R, et al. An open label study to assess the impact of testosterone replacement and withdrawal on sexual function, psychological symptoms and mobility in severely obese hypogonadal men. *16th Annual Congress of the European Society for Sexual Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey. Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine* 2014.
12. Aversa A, Francomano D, Bruzziches R, et al. CAG repeat length and arterial reactivity after acute testosterone gel administration in men with severe hypogonadism. *15th Congress of the European Society for Sexual Medicine Amsterdam Netherlands. Conference Start: 20121206 Conference End: 20121208. Journal of Sexual Medicine* 2012;9:321
13. Aversa A, Francomano D, Bruzziches R, et al. Effects of testosterone replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men. *16th Annual Congress of the European Society for Sexual Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey. Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine* 2014.
14. Aversa A, Francomano D, Bruzziches R, et al. Metabolic changes induced by testosterone undecanoate in middle-aged men with hypogonadal-metabolic syndrome: Results of 104 weeks placebo-controlled treatment *12th Annual Meeting of the European Society for Sexual Medicine Lyon France. Conference Start: 20091115 Conference End: 20091118. Journal of Sexual Medicine* 2009;6:415.
15. Aversa A, Francomano D, Ilacqua A, et al. Effects of five-years treatment with testosterone undecanoate on urinary function in hypogonadal men with metabolic syndrome. *16th Annual Congress of the European Society for Sexual*

- Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey. Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine 2014.*
16. Aversa A, Francomano D., R. Bruzziches, M. Natali, E. Greco, P. Pezzella, G. Spera. Body composition and psychological changes induced by long acting testosterone undecanoate in middle-aged men with hypogonadal-metabolic syndrome: Results of 104 weeks placebo-controlled treatment. *12th Annual Meeting of the European Society for Sexual Medicine Lyon France. Conference Start: 20091115 Conference End: 20091118. Journal of Sexual Medicine 2009;6:439*
 17. Avila A, Gittens PR, Hwang K, et al. Low dose human chorionic gonadotropin prevents azoospermia and maintains fertility in hypogonadal men on testosterone replacement therapy. *Annual Meeting of the American Society for Reproductive Medicine, ASRM 2010 Denver, CO United States. Conference Start: 20101023 Conference End: 20101027. Fertility and Sterility 2010;94(4 Suppl 1):S12.*
 18. Baillargeon J. Risk of cardiac events in older men receiving testosterone replacement therapy. *46th Annual Society for Epidemiologic Research, SER Meeting Boston, MA United States. Conference Start: 20130618 Conference End: 20130621. American Journal of Epidemiology 2013;177:S175.*
 19. Balbontin F, Moreno S, Morgentaler A. Effect of long-acting testosterone injections for treatment of hypogonadism after brachytherapy for prostate cancer. *2011 Annual Meeting of the American Urological Association, AUA Washington, DC United States. Conference Start: 20110514 Conference End: 20110519. Journal of Urology. 2011;185(4 Suppl 1):e673.*
 20. Balouly K, Sobotka V, Snajderova M, et al. Comparison of quality of life according to IPSS, AMS and IIEF scores during hormone replacement therapy by testosterone in men with primary hypogonadism. *EAU 10th Central European Meeting, CEM Bratislava Slovakia. Conference Start: 20101022 Conference End: 20101023. European Urology 2010;9(6):641.*
 21. Balouly K., Urban M, Sobotka V, et al. Prostatic cyst as a new finding in patients with Kallmann syndrome treated by long term testosterone replacement therapy. *EAU 11th Central European Meeting, CEM Timisoara Romania. Conference Start: 20111028 Conference End: 20111029. European Urology 2011;10(9):624.*
 22. Bodhani A, Kallenbach L, Vasey J, et al. Effect of testosterone gel on symptom burden and medication use in patients with hypogonadism: A retrospective cohort study. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:241*
 23. Bokhamada HK, Dalton CF, Woodroffe MN, et al. The effect of testosterone replacement therapy on serum pro-and anti-inflammatory biomarkers and apolipoprotein levels in hypogonadal men with diabetes. *20th European Congress on Obesity, ECO 2013 Liverpool United Kingdom. Conference Start: 20130512 Conference End: 20130515. Obesity Facts. 2013;6:141*
 24. Boxer A, Small K, Tamler R, et al. Safety and efficacy of testosterone supplementation in men with chronic liver disease. *61st Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2010 Boston, MA United States. Conference Start: 20101029 Conference End: 20101102. Hepatology 2010;52.*
 25. Brooke JC, McLaren DS, Walter DJ, et al. Cardiovascular safety and testosterone replacement therapy in male hypogonadism including men with type 2 diabetes and cardiovascular disease. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3 Meeting Abstracts).*
 26. Brooke JC, Walter DJ, Muraleedharan V, et al. Testosterone replacement therapy in hypogonadal men with Type 2 diabetes reduces HbA1c, total cholesterol, liver transaminases and systolic blood pressure: An audit of clinical practice. *Diabetes UK Professional Conference 2012 Glasgow United Kingdom. Conference Start: 20120307 Conference End: 20120309. Diabetic Medicine. 2012;29:70.*
 27. Bryant A, Hoppe BS, Mendenhall NP, et al. Testosterone replacement therapy in men with prostate cancer after proton therapy. *2014 Genitourinary Cancers Symposium San Francisco, CA United States. Conference Start: 20140130 Conference End: 20140201. Journal of Clinical Oncology 2014;32(4 Suppl 1).*
 28. Burnett AL, Miller M, Kan-Dobrosky N. Testosterone replacement and priapism risk: No definite relationship. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine 2012;9:20.*
 29. Buvat J, Arver S, Behre H, et al. A placebo controlled study of the effects on insulin sensitivity and sexual function of transdermal testosterone gel in hypogonadal men with type II diabetes and/or metabolic syndrome: Data from the times 2 study. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine 2009;6:56.*
 30. Buvat J, Maggi M, Porst H, et al. What is the threshold level of the PDE5 inhibitors' testosterone-dependence in men? A double blind placebo-controlled trial of testosterone gel addition in men with ed non responding to tadalafil 10 Mg once a day alone. *24th Annual Congress of the European Association of Urology, EAU Stockholm Sweden. Conference Start: 20090317 Conference End: 20090321. European Urology 2009;8(4):214.*
 31. Buvat J, Montorsi F, Cuzin B, et al. From which serum testosterone level should we add testosterone therapy to men with erectile dysfunction not responding to PDE5 inhibitors alone? A double blind placebo-controlled trial of testosterone gel addition to men not responding to tadalafil once a day alone. *2009 American Urological Association*

- (AUA) Annual Meeting Chicago, IL United States. Conference Start: 20090425 Conference End: 20090430. *Journal of Urology* 2009;181(4 Suppl 1):488.
32. Cavender RK, Fairall M, Vorhees WF. Subcutaneous testosterone pellet implant therapy in the United States for men with testosterone deficiency syndrome: A single-site retrospective safety and efficacy study. 2009 American Urological Association (AUA) Annual Meeting Chicago, IL United States. Conference Start: 20090425 Conference End: 20090430. *Journal of Urology* 2009;181(4 Suppl 1):488.
 33. Cedres S, Serra P, Palasti S, et al. Effects of testosterone replacement therapy on glucose homeostasis, visceral obesity and sexual function in middle-aged men with type 2 diabetes and androgen deficiency. 14th World Meeting of the International Society for Sexual Medicine Seoul South Korea. Conference Start: 20100926 Conference End: 20100930. *Journal of Sexual Medicine* 2010;7:163.
 34. Chiles A, Provet J, Honig S. Injection site abscess with unpredictable testosterone response is an uncommon complication of testosterone pellet implantation. 17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. *Journal of Sexual Medicine* 2012;9:20.
 35. Chitale S, Banerjee S, Hull S, et al. Testosterone and prostate cancer/rising PSA: Is the link getting weaker and the picture clearer? 15th Congress of the European Society for Sexual Medicine Amsterdam Netherlands. Conference Start: 20121206 Conference End: 20121208. *Journal of Sexual Medicine* 2012;9:318.
 36. Cirmigliaro CM, Moyer J, LaFountaine M, et al. Lean tissue mass increases from physiological testosterone replacement therapy in hypogonadal men with SCI. Congress on Spinal Cord Medicine and Rehabilitation Dallas, TX United States. Conference Start: 20090923 Conference End: 20090926. *Journal of Spinal Cord Medicine* 2009;32(4):471-472.
 37. Connors W, Di SS, Flinn K, et al. Effect of baseline testosterone on one and three month testosterone levels with testosterone pellet therapy. 17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. *Journal of Sexual Medicine* 2012;9:19.
 38. Connors W, Mousseau G, Flinn K, et al. Testosterone pellet therapy after prostate cancer. 15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. *Journal of Sexual Medicine* 2010;47:1.
 39. Connors W, Rhoden EL, Morgentaler A. Symptomatic improvement in libido and likelihood of completing 12 months of testosterone therapy. 15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. *Journal of Sexual Medicine* 2010;47:1.
 40. Connors W, Flinn K, Morgentaler A. Subcutaneous testosterone injection is effective and well-tolerated. *Journal of Sexual Medicine*. Conference: 16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. *Journal of Sexual Medicine* 2011;8.
 41. Corona B, Maggi M. Re: Testosterone replacement therapy in the setting of prostate cancer treated with radiation. *European Urology* 2013;63(3):583
 42. Cortada J, Becerra A. Evidence for late-onset hypogonadism (LOH) in the Spanish population: Effectiveness and safety of replacement treatment. ISMH World Congress 2010 Nice France. Conference Start: 20101028 Conference End: 20101030. *Journal of Men's Health* 2010;7(3):308.
 43. Coward R, Simhan J, Pruthi R, et al. Racial differences in hypogonadal improvement and prostate-specific antigen in hypogonadal men treated with testosterone replacement therapy. 15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. *Journal of Sexual Medicine*. 2010;47:4.
 44. Davila A, Weber T, Arison C, et al. PSA response after testosterone supplementation in patients who have previously received radiation or surgical therapy for their localized prostate cancer. 15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. *Journal of Sexual Medicine* 2010;47:1.
 45. De Mara LS, Lineburge AA, Ulbrich AZ, et al. The effect of high-intensity exercise and testosterone supplementation in men with heart failure. *Global Heart. World Congress of Cardiology Scientific Sessions 2014, WCC 2014 Melbourne, VIC Australia*. Conference Start: 20140504 Conference End: 20140507; 2014:e71
 46. Debruyne F, Roehrborn C, Schroder F, et al. Testosterone and key aspects of physical and emotional health in untreated hypogonadal men: Baseline findings from the registry of hypogonadism in men (RHYME). 33rd Congress of the Societe Internationale d'Urologie Vancouver, BC Canada. Conference Start: 20130908 Conference End: 20130912. *Urology* 2013;82(3 Suppl 1):S282-S283.
 47. Del EF, Garcia J, DeBakey ME, et al. A double-blind placebo controlled trial of testosterone replacement for fatigue in males with advanced cancer (TH307-B). Annual Assembly of the American Academy of Hospice and Palliative Medicine and the Hospice and Palliative Nurses Association, AAHPN/NPNA 2013 New Orleans, LA United States. Conference Start: 20130313. *Journal of Pain and Symptom Management* 2013;336

48. Del FE, Garcia J, Dev R, et al. Testosterone replacement for fatigue in male hypogonadic patients with advanced cancer: A preliminary double-blind, placebo-controlled trial. *Supportive Care in Cancer. 2012 International MASCC/ISOO Symposium: Supportive Care in Cancer New York City, NY United States.*Conference Start: 20120628 Conference End: 20120630; 20:pp S249-S250
49. Douaihy Y, Yassin DJ, Hakimian P, et al. Lower urinary tract symptoms improve with testosterone replacement therapy in men with late onset hypogonadism. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States.*Conference Start: 20120519 Conference End: 20120523. *Journal of Urology* 2012;187(4 Suppl 1):e605.
50. Douaihy Y, El.P. Hakimian,R. Pinkhasove,A.D.-J. Yassin,A. Yassin,R. Shabsigh. Long-term testosterone improves all the domains of metabolic syndrome. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States.*Conference Start: 20120519 Conference End: 20120523. *Journal of Urology* 2012;187(4 Suppl 1):e604.
51. Eisenberg M, Betts P, Herder D, et al. Testosterone replacement therapy and cancer risk. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States.*Conference Start: 20130504 Conference End: 20130508. *Journal of Urology* 2013;189(4 Suppl 1):e617.
52. El DY, Shabsigh R, Yassin A, et al. Long-term testosterone treatment in hypogonadal men improves all components of the metabolic syndrome. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States.*Conference Start: 20120623 Conference End: 20120626. *Endocrine Reviews* 2012;33(3 Meeting Abstracts).
53. El DY, Shabsigh R, Yassin A, et al. Testosterone therapy with testosterone undecanoate long-acting intramuscular injections in hypogonadal men is associated with reduction in obesity. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States.*Conference Start: 20120623 Conference End: 20120626. *Endocrine Reviews* 2012;33(3 Meeting Abstracts).
54. El DY, Yassin ADJ, Pinkhasov R, et al. Testosterone replacement therapy with testosterone undecanoate long acting intramuscular injections is associated with reduction in obesity. *27th Annual Congress of the European Association of Urology, EAU Paris France.* Conference Start: 20120224 Conference End: 20120228. *European Urology* 2012;11(1):e590.
55. Ely BR, Miner JA, Miner JC, et al. Flow-mediated dilation responses to exogenous testosterone administration in healthy males. *Experimental Biology 2013, EB Boston, MA United States.*Conference Start: 20130420 Conference End: 20130424. *FASEB Journal* 2013;27.
56. Engineer D, Cardwell G, Bruera E, et al. A preliminary trial of testosterone replacement for fatigue in male hypogonadal patients with advanced cancer. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States.* Conference Start: 20120623 Conference End: 20120626. *Endocrine Reviews* 2012;33
57. F. Saad,S.Y. Kalinchenko,Y.A. Tishova,L.J. Gooren,E.J. Giltay. Long-term effects of normalization of testosterone on variables of the metabolic syndrome in hypogonadal men: The moscow study. *4th International Congress on Prediabetes and the Metabolic Syndrome Madrid Spain.*Conference Start: 20110406 Conference End: 20110409. *Journal of Diabetes* 2011;3:153
58. Fabbro E, Del,J. Garcia,R. Dev,J.L. Palmer,C. Klingner-Winton,L.E. Roberts,J. Allo,G. Cardwell,E. Bruera. A randomized placebo-controlled trial of testosterone replacement for fatigue in male hypogonadic patients with advanced cancer. *ASCO Annual Meeting 2011 Chicago, IL United States.*Conference Start: 20110603 Conference End: 20110607. *Journal of Clinical Oncology* 2011;29(15 Suppl 1)
59. Fahrleitner-Pammer A, Obermayer-Pietsch B, Wagner D, et al. Testosterone replacement in cardiac transplant patients on top of bisphosphonate therapy exerts multiple benefits on bone mass, libido and sexual activity: A 5-year prospective study. *15th Jahrestagung der Österreichischen Gesellschaft für Endokrinologie und Stoffwechsel Wien Austria.*Conference Start: 20100507 Conference End: 20100508. *Austrian Journal of Clinical Endocrinology and Metabolism* 2010.
60. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Obermayer-Pietsch BM, et al. Testosterone replacement in combination with bisphosphonate therapy in male cardiac transplant patients exerts additional benefits on bone mass: A 5-year prospective study. *36th European Symposium on Calcified Tissues, ECTS 2009 Vienna Austria.*Conference Start: 20090523 Conference End: 20090527 *Bone* 2009.
61. Farid S, Ahmad H, Gheorghe D, et al. Side effect profile of long-term treatment of elderly hypogonadal men with testosterone undecanoate. *International Journal of Urology.*Conference: *11th Asian Congress of Urology of the Urological Association of Asia, ACU 2012 Pattaya Thailand.*Conference Start: 20120822 Conference End: 20120826. *International Journal of Urology* 2012;19:202.
62. Farid S, Ahmad H, Gheorghe D, et al. Testosterone treatment up to 5 years in elderly, hypogonadal men has profound favourable effects on body weight and waist circumference. *11th Asian Congress of Urology of the Urological Association of Asia, ACU 2012 Pattaya Thailand.*Conference Start: 20120822 Conference End: 20120826. *International Journal of Urology* 2012;19:202.
63. Farid S, Ahmad H, Gheorghe D, et al. Testosterone treatment with injectable testosterone undecanoate sustainably improves erectile function, urinary function and quality of life in elderly hypogonadal patients over 5 years. *11th*

- Asian Congress of Urology of the Urological Association of Asia, ACU 2012 Pattaya Thailand. Conference Start: 20120822 Conference End: 20120826. International Journal of Urology 2012;19:202.*
64. Farid S, Aksam Y, Ahmad H, et al. "Late onset hypogonadism" is an interdisciplinary condition-comorbidities in elderly hypogonadal men presenting or referred to urological institutions in Germany. *11th Asian Congress of Urology of the Urological Association of Asia, ACU 2012 Pattaya Thailand. Conference Start: 20120822 Conference End: 20120826. International Journal of Urology 2012;19:85.*
 65. Farid S, Doros G, Haider A, et al. Long-term treatment of middleaged to elderly hypogonadal men with testosterone undecanoate does not indicate an increased risk of prostate cancer. *Journal of Sexual Medicine. Conference: 15th Congress of the European Society for Sexual Medicine Amsterdam Netherlands. Conference Start: 20121206 Conference End: 20121208. Conference Publication: (var.pagings).9 ()(pp 354), 2012. Date of Publication: D. 2012///. #volume#: #pages#*
 66. Farid S, Doros G, Traish A, et al. Most hypogonadal men are obese; long-term testosterone treatment leads to continuous and sustained reductions of body weight and waist circumference. *15th Congress of the European Society for Sexual Medicine Amsterdam Netherlands. Conference Start: 20121206 Conference End: 20121208. Journal of Sexual Medicine 2012;9:365.*
 67. Farid S, Haider A, Yassin A. "late onset hypogonadism" is not an isolated condition-comorbidities in elderly hypogonadal men presenting or referred to urological institutions in germany. *15th Congress of the European Society for Sexual Medicine Amsterdam Netherlands. Conference Start: 20121206 Conference End: 20121208. Journal of Sexual Medicine 2012;9:322-323.*
 68. Frederiksen L, Hojlund K, Hougaard DM, et al. Testosterone therapy decreased adiponectin and subcutaneous fat in aging men. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32*
 69. Frederiksen L, Hougaard DM, Brixen K, et al. Testosterone gel significantly increase lean body mass in ageing males with relatively low bio-available testosterone and waist circumference above 94 cm: A double blinded, randomized, placebo controlled 6 months study. *12th European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:672*
 70. Giannetta E, Isidori AM, Pierotti S, et al. Testosterone replacement improves metabolic syndrome and inflammation independently of body fat mass changes. *6th European Congress of Andrology Athens Greece. Conference Start: 20100929 Conference End: 20101001 International Journal of Andrology 2010;33:57*
 71. Giltay EJ, Tishova Y, Mskhalaya G, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome: The Moscow Study. *12th European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:524*
 72. Giltay EJ, Tishova YA, Mskhalaya GL, et al. Effects of testosterone supplementation on depressive symptoms in hypogonadal men with the metabolic syndrome: The Moscow study. *18th European Congress of Psychiatry Munich Germany. Conference Start: 20100227 Conference End: 20100302. European Psychiatry. 2010;25.*
 73. Glinborg D, Nielsen TL, Frederiksen L, et al. Quality of life, testosterone and abdominal obesity in 779 young and 598 aging men. Effects of randomized testosterone treatment on quality of life in 38 aging men with relative hypogonadism. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33*
 74. Gluud A. Effect of testosterone treatment in men with alcoholic cirrhosis [EASL abstract]. *Journal of Hepatology 1985;1:S59.*
 75. Gold SM, Chalifoux S, Giesser BS, et al. Immune modulation and increased neurotrophic factor production in multiple sclerosis patients treated with testosterone. *Journal of Neuroinflammation 2008;5:32.*
 76. Goldstein I. Safety assessment of men and women with hypogonadism treated with long-acting subcutaneous testosterone pellets: A three-year study. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine 2011;8.*
 77. Goldstein I. Subcutaneous testosterone pellet implant (TESTOPEL) Therapy for men and women with testosterone deficiency syndrome: A single-site retrospective safety analysis. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine 2010;47:1.*
 78. Gooren LJ, Bouloux PM, Giltay EJ, Saad F. The effect of 6 months' treatment with testosterone gel versus placebo on body composition and health-related quality of life in hypogonadal men. *4th International Congress on Prediabetes and the Metabolic Syndrome Madrid Spain. Conference Start: 20110406 Conference End: 20110409. Journal of Diabetes 2011;3:147*
 79. Gottardo F, Grunwald L, Secker A, et al. Hypogonadism in long-term survivors with previous germ cell tumors. *22th Jahrestagung der Deutschen Gesellschaft für Andrologie e.V. Hamburg Germany. Conference Start: 20101029 Conference End: 20101031. Journal für Reproduktionsmedizin und Endokrinologie 2010;7(5):443.*

80. Griend JPV, Nakamura TK, Barry TD, et al. Targeting testosterone concentrations in elderly males using transdermal testosterone gel. *2011 Annual Meeting of the American College of Clinical Pharmacy Pittsburgh, PA United States. Conference Start: 20111016 Conference End: 20111019. Pharmacotherapy* 2011;31(10):339e
81. Habous M, Badwan A, Elborai S, et al. Are the alternative therapy for hypogonadism as effective as conventional testosterone(T) therapy. *International Symposium on Prostate, Androgens and Men's Sexual Health 2013 Berlin Germany. Conference Start: 20130621 Conference End: 20130623 Journal of Sexual Medicine* 2013; 10:260
82. Hackett G. Long-acting testosterone undecanoate improved aging male symptom scores but not depression vs. placebo in a hypogonadal population with type 2 diabetes. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:403
83. Hackett G. Long-acting testosterone undecanoate improved diabetes control vs. placebo in a hypogonadal population with type 2 diabetes. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:430
84. Hackett GI, Bhartia M, Cole N. Depression significantly reduces the response to testosterone therapy in men with type 2 diabetes and hypogonadism. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:240
85. Hackett GI, Bhartia M, Cole N. Metabolic and symptomatic response to testosterone undecanoate in men with type 2 diabetes and hypogonadism takes 12 to 18 months to maximum effect. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:205
86. Haider A, Doros G, Traish A. Best abstract: Effects of long-term testosterone therapy on prostate, urinary and sexual parameters in 300 hypogonadal men treated for up to 6 years. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology* 2014;191(4 Suppl 1):e221
87. Haider A, Traish A. Effects of long-term testosterone treatment in obese hypogonadal men on body weight and prostate parameters. *33rd Congress of the Societe Internationale d'Urologie Vancouver, BC Canada. Conference Start: 20130908 Conference End: 20130912. Urology* 2013;82(3 Suppl 1):S30.
88. Haider A, Yassin A, Gooren L, et al. "Late onset hypogonadism" is not an isolated condition-comorbidities in elderly hypogonadal men presenting or referred to urological institutions in Germany. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33(3 Meeting Abstracts).
89. Haider A, Zitzmann M, Yassin A. Long-term treatment with testosterone undecanoate injections and its effect of prostate cancer incidence in hypogonadal men. *2014 Genitourinary Cancers Symposium San Francisco, CA United States. Conference Start: 20140130 Conference End: 20140201. Journal of Clinical Oncology* 2014;32(4 Suppl 1).
90. Hakobyan S. Clinical study of testosterone gel as adjunctive therapy to tadalafil in hypogonadal men with erectile dysfunction. *International Symposium on Prostate, Androgens and Men's Sexual Health 2013 Berlin Germany. Conference Start: 20130621 Conference End: 20130623. Journal of Sexual Medicine* 2013; 10:267
91. Ho CCK, Tong SF, Low WY, et al. A randomized double blind placebocontrolled trial assessing quality of life via aging male symptoms (AMS) scale after treatment with intramuscular long-acting testosterone. *13th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kaohsiung Taiwan (Republic of China). Conference Start: 20111116 Conference End: 20111120. Journal of Sexual Medicine.*2012;9:144.
92. Ho CCK, Tong SF, Low WY, et al. Assessing quality of life via aging male symptoms (AMS) scale after treatment with intramuscular long-acting testosterone. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:403
93. Hoang, Durham W, Casperson S, et al. Elevation of testosterone concentrations in the low normal range reduces fatigue in older men. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33(3).
94. Hoyos A, Yee B, Phillips C, et al. Longer-term effects of testosterone therapy on sleep, breathing and body composition in obese men with obstructive sleep apnea (OSA) undergoing weight loss: A randomised placebo controlled 18 week trial. *22nd Annual Scientific Meeting of the Australian Sleep Association and Australian Sleep Technologists Association: Sleep Down Under 2010 - Biodiversity of Sleep Christchurch New Zealand. Conference Start: 20101021. Sleep and Biological Rhythms* 2010.
95. Hoyos A, Yee B, Phillips C, et al. Longer-term effects of testosterone therapy on sleep, breathing and body composition in obese men with obstructive sleep apnea (OSA) undergoing weight loss: A randomised placebo controlled 18 week trial [abstract]. *Sleep and biological rhythms* 2010;8:A47.
96. Hoyos CM, Yee BJ, Phillips CL, et al. Longer-term effects of testosterone therapy on sleep, breathing and body composition in obese men with OSA undergoing weight loss: A randomized placebo-controlled trial [abstract]. *Journal of Sleep Research* 2010;19:17.
97. Hoyos CM, Yee BY, Phillips CL, et al. Longer-term effects of testosterone therapy on sleep, breathing and body composition in obese men with obstructive sleep apnea (OSA) undergoing weight loss: A randomised placebo

- controlled 18 week trial. *11th International Congress on Obesity, ICO 2010 Stockholm Sweden. Conference Start: 20100711 Conference End: 20100715 Obesity Reviews 2010;11(11):824-825.*
98. Hoyos CM, Yee BY, Phillips CL, et al. Longer-term effects of testosterone therapy on sleep, breathing and body composition in obese men with OSA undergoing weight loss: A randomized placebo-controlled trial. *20th Congress of the European Sleep Research Society Lisbon Portugal. Conference Start: 20100914 Conference End: 20100918. Journal of Sleep Research 2010;19:17*
 99. Hsieh TC, Pastuszak A, Aghazadeh M, et al. Elevated dihydrotestosterone is associated with testosterone-induced erythrocytosis. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology 2013;189(4 Suppl 1):e618.*
 100. Hua JT, Rojas DC, Filley CM, et al. Structural brain mri changes following testosterone supplementation in healthy older men. *American Federation for Medical Research Western Regional Meeting, AFMR 2013 Carmel, CA United States. Conference Start: 20130123 Conference End: 20130126. Journal of Investigative Medicine 2013;61(1): 148*
 101. Huang G, Bhasin S, Tang E, et al. Effect of testosterone administration on hepatic fat and insulin resistance in older men in a placebo-controlled randomized trial. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33*
 102. Hult M, Morgentaler A. Testosterone therapy in men on active surveillance for prostate cancer. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology 2013;189(4 Suppl 1):e271.*
 103. Jones H, Behre H, Channer K, et al. An international study of testosterone (T) gel in hypogonadal men with type II diabetes (T2D) and/or metabolic syndrome (METS, IDF criteria): The Times 2 study. *3rd International Congress on Prediabetes and the Metabolic Syndrome Nice France. Conference Start: 20090401 Conference End: 20090404. Journal of Diabetes 2009;1:A37-A38.*
 104. Jones H, Howell J, Channer K.. Testosterone improves glycaemic control, insulin resistance, body fat and sexual function in men with the metabolic syndrome and/or type 2 diabetes: A multicentre European clinical trial: The TIMES2 study. *Society for Endocrinology, British Endocrine Societies, BES 2010 Manchester United Kingdom. Conference Start: 20100315 Conference End: 20100318. Endocrine Abstracts 2010;21:16.*
 105. Jones TH. More than 8 years of experience in treating men with type 2 diabetes with testosterone. *6th World Congress on Men's Health (WCMH) Vienna Austria. Conference Start: 20091009 Conference End: 20091011. Journal of Men's Health. 2009;6(4):398.*
 106. Kacker R, Hult M, Connors W, et al. Safety of testosterone therapy in men with prostate cancer. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e529-e530.*
 107. Kalinchenko S, Tishova Y, Mskhalaya G, et al. Effects of parenteral testosterone undecanoate administration on inflammatory markers: The Moscow study. *12th European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:682.*
 108. Kalinchenko S, Tishova Y, Mskhalaya G, et al. The Moscow study: A randomized, placebo-controlled, double-blind trial of parenteral testosterone undecanoate on the metabolic syndrome and inflammation markers. *12th Biennial Meeting of the Asia Pacific Society for Sexual Medicine, Singapore. Conference Start: 20091212 Conference End: 20091215. Journal of Sexual Medicine 2010;47:103.*
 109. Kalinchenko SY, Tishova YA, Mskhalaya GZ, et al. Obesity and androgen deficiency in men - Moscow study. *6th World Congress on Men's Health (WCMH) Vienna Austria. Conference Start: 20091009 Conference End: 20091011. Journal of Men's Health 2009;6(4):398.*
 110. Kaplan AL, Gu X, Hu JC. Testosterone replacement therapy following the diagnosis of prostate cancer: Outcomes and utilization trends. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology 2013;189(4 Suppl 1):e95.*
 111. Kashanian A, El DY, Gosh P, et al. Testosterone replacement therapy improves glucose control through weight loss and waist circumference reduction. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States. Conference Start: 20120519 Conference End: 20120523. Journal of Urology 2012;187(4 Suppl 1):e604.*
 112. Katz A, Akhavan A, Park K, et al. Sustained efficacy and safety with long-term clomiphene citrate. *2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA United States. Conference Start: 20100529 Conference End: 20100603. Journal of Urology 2010;183(4 Suppl 1):e532*
 113. Katz DJ, Matsushita K, Stember DS, et al. Long-term follow-up of the safety and efficacy of Testosterone Replacement Therapy (TRT) following Radical Prostatectomy (RP). *66th Annual Scientific Meeting of the Urological Society of Australia and New Zealand Melbourne, VIC Australia. Conference Start: 20130413 Conference End: 20130416. BJU International 2013;111:25-26.*
 114. Kaufman JM, Brennan JJ, Garwin JL, et al. Pharmacokinetics and efficacy of a 1.62% testosterone gel for the treatment of hypogonadal men: Secondary efficacy results from a phase III study. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine 2011;8.*

115. Kaufman JM, Brennan JJ, Garwin JL, et al. The efficacy and safety of a 1.62% testosterone gel for the treatment of hypogonadal men: Primary efficacy results from a phase III study. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
116. Kaufman JM, Miller MG, Fitzpatrick S, et al. One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: Secondary efficacy results. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
117. Kaufman JM, Miller MG, Fitzpatrick S, et al. One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: Primary efficacy results. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
118. Khera M, Miner M, Bhattacharya R, et al. PSA levels significantly rise after 3 months of testosterone replacement therapy in severely hypogonadal men in the testim registry in the US (TRIUS) cohort. *2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA United States. Conference Start: 20100529 Conference End: 20100603. Journal of Urology* 2010;183(4 Suppl 1):e533
119. Khera M, Miner M, Bhattacharya R, et al. Sexual function significantly improved in hypogonadal men with erectile dysfunction (ED) after testosterone replacement therapy (TRT): 6-month results from the testim registry in the us (trius) cohort. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
120. Khera M, Miner MM, Bhattacharya RK, et al. PSA levels significantly rise after 6 months of testosterone replacement therapy in severely hypogonadal men in the testim registry in the US (TRiUS) cohort. *ISMH World Congress 2010 Nice France. Conference Start: 20101028 Conference End: 20101030. Journal of Men's Health* 2010;7(3):348.
121. Khurana K, Shoskes D. Real-world experience with testosterone pellets for testosterone deficiency syndrome (TDS). *International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and the 69th Annual Meeting of the American Society for Reproductive Medicine, IFFS-ASRM 2013 Boston, MA United States. Fertility and Sterility* 2013;S212
122. Kim J, Ham BK, Yang DY, et al. Effect of daily tadalafil and monthly testosterone enanthate on PDE5 Inhibitor nonresponders. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:436-437.
123. Konaka H, Sugimoto K, Shigehara K, et al. Androgen replacement therapy improves high-molecular weight adiponectin status in patients with late-onset hypogonadism. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan. Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine* 2013;10:231
124. Konaka H, Sugimoto K, Shigehara K, et al. Androgen replacement therapy improved high-molecular weight adiponectin status in patients with late-onset hypogonadism. *32nd Congress of the Societe Internationale d'Urologie Fukuoka Japan. Conference Start: 20120930 Conference End: 20121004. Urology* 2012;80(3 Suppl 1):S246
125. Konaka H, Sugimoto K, Shigehara K, et al. Effects of long-term androgen replacement therapy on physical and mental status in aging males with late-onset hypogonadism: Results of a phase iii, multicenter, randomized, controlled trial. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology* 2013;189:(4 Suppl 1):e506
126. Krasnow RE, Eisenberg ML, Walters RC, et al. Etiology of profound hypogonadism in a large, contemporary cohort. *Journal of Sexual Medicine. Conference: 16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
127. Kryger AH. Testocrema, a unique high-potency transdermal hormone cream. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33
128. Lachaine J, Beauchemin C, Lapierre ME, et al. Utilization trends of various formulations of testosterone: An analysis of the RAMQ database. *ISPOR 18th Annual International Meeting New Orleans, LA United States. Conference Start: 20130518 Conference End: 20130522. Value in Health* 2013;16(3):A175
129. Lanes S, Curtis BH, Wentworth C, et al. Management of comorbid type 2 diabetes and low testosterone in primary care (UK). *73rd Scientific Sessions of the American Diabetes Association Chicago, IL United States. Conference Start: 20130621 Conference End: 20130625. Diabetes* 2013;62:A392.
130. Lapauw BM, Ouwens DM, Hart LMT, et al. Short-term changes in serum sex steroid levels directly affect insulin sensitivity in healthy young men. *69th Annual Meeting of the American Diabetes Association New Orleans, LA United States. Conference Start: 20090605 Conference End: 20090609. Diabetes* 2009;58.

131. Lee HS, Bahn G, Azad N. The effect of testosterone replacement on glycemic control in hypogonadal men with type 2 diabetes mellitus. *71st Scientific Sessions of the American Diabetes Association San Diego, CA United States. Conference Start: 20110624 Conference End: 20110628. Diabetes* 2011;60:A627.
132. Levine L., Levine LA. Clomiphene citrate versus testosterone gel replacement therapy for hypogonadism: Efficacy and treatment cost. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine.*2009;6:81
133. Ljunggren A, Hedelin H, Stroberg P. Effects on prostate size and voiding symptoms in men with late-onset-hypogonadism (LOH) using gel testosterone-replacement-therapy (T-R-T) a one year follow-up. *24th Annual Congress of the European Association of Urology, EAU Stockholm Sweden. Conference Start: 20090317 Conference End: 20090321. European Urology* 2009;8(4):235.
134. M. Khera, M. Miner, R. Bhattacharya, G. Blick, H. Kushner, D. Nguyen. Correlation of sexual function domains with testosterone levels in men with erectile dysfunction in the trius cohort. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:1.
135. M. Sand, B. Moclair, M. Hemani, J. Kaminetsky. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for treatment of male hypogonadism. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
136. Maggio M, Ceda G, Milaneschi Y, et al. Effects of testosterone treatment on inflammatory markers in older men. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews* 2011;32
137. Maggio M, Ceda G, Milaneschi Y, et al. Is the hematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews* 2011;32
138. Mamedov M, Sharvadze G, Kontsevaya A, et al. Effect of hormone replacement therapy on cardiometabolic profile of men with hypogonadism and high cardiovascular risk. *4th International Congress on Prediabetes and the Metabolic Syndrome Madrid Spain. Conference Start: 20110406 Conference End: 20110409. Journal of Diabetes* 2011;3:151.
139. Matsushita K, Katz D, Nelson C, et al. LH suppression profile in men treated with exogenous testosterone. *International Symposium on Prostate, Androgens and Men's Sexual Health 2013 Berlin Germany. Conference Start: 20130621 Conference End: 20130623. Journal of Sexual Medicine* 2013;10:267.
140. Matsushita K, Katz D, Stember D, et al. Long-term follow-up of the safety and efficacy of testosterone replacement therapy following radical prostatectomy. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States. Conference Start: 20120519 Conference End: 20120523. Journal of Urology* 2012;187(4 Suppl 1):e602-e603.
141. Matsushita K, Katz DJ, Bernstein M, et al. LH suppression profiles in men treated with exogenous testosterone. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:280-281.
142. Matsushita K, Katz DJ, Stember DS, et al. Analysis of the safety and efficacy of testosterone supplementation following radical prostatectomy. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:205
143. Mazo EB, Gamidov SI, Sotnikova EM. Effect of combined therapy with testosterone undecanoate and vardenafil on erectile and endothelial function in hypogonadal men with erectile dysfunction. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine* 2009;6:57.
144. Mazzola A, Berookhim BM, Katz D, et al. The impact on hypogonadal symptoms of switching from clomiphene citrate (CC) to transdermal testosterone (TDT). *International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and the 69th Annual Meeting of the American Society for Reproductive Medicine, IFFS-ASRM 2013 Boston, MA United States. Fertility and Sterility* 2013:S209.
145. McCarty E, Fyfe J, Dinsmore W. An audit of 871 serum testosterone levels at a sexual dysfunction clinic over 20 years. *ISMH World Congress 2010 Nice France. Conference Start: 20101028 Conference End: 20101030. Journal of Men's Health* 2010;7(3):327.
146. McCarty E, Fyfe J, Emerson C, et al. An audit of 871 serum testosterone tests at a sexual dysfunction clinic. *2nd Joint Conference of the British HIV Association and the British Association for Sexual Health and HIV Manchester United Kingdom. Conference Start: 20100420 Conference End: 20100423. HIV Medicine* 2010;11.
147. McCullough A, Khera M, Hellstrom W, et al. A multi-institutional observational study on testosterone levels after testosterone pellet (testopel TM) insertion. *ISMH World Congress 2010 Nice France. Conference Start: 20101028 Conference End: 20101030. Journal of Men's Health* 2010;7(3):319.
148. McCullough A, Khera M, Hellstrom W, et al. A multi-institutional observational study on testosterone levels after testosterone pellet (TESTOPELTM) insertion. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of*

- North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. *Journal of Sexual Medicine* 2010;47:1.
149. McCullough A, Khera M, Hellstron W, et al. A multi-institutional observational study on testosterone levels after testosterone pellet (Testopel) insertion. *2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA United States. Conference Start: 20100529 Conference End: 20100603. Journal of Urology* 2010;183(4 Suppl 1):e577.
 150. McCullough A. The effect of testosterone pellet (TESTOPEL) insertion on pituitary gonadotropins. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:1.
 151. McLaren DS, Brooke JC, Walter DJ, et al. Long-term effects of testosterone replacement therapy on cardiovascular risk factors in hypogonadism, including men with cardiovascular disease and/or type 2 diabetes. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33
 152. Miller J, Britto M, Fitzpatrick S, et al. Single and multiple dose pharmacokinetics of testosterone in hypogonadal males after application of 1.62% testosterone gel. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
 153. Miller J, Britto M, Fitzpatrick S, et al. The effect of concomitant application of moisturizer lotion or sunscreen on the bioavailability of 1.62% testosterone gel in hypogonadal males. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
 154. Miller J, Britto M, Fitzpatrick S, et al. The effect of varying the application site on the bioavailability of 1.62% testosterone gel in hypogonadal males. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
 155. Miner M, Khera M, Bhattacharya RK, et al. Testim registry in the United States (TRIUS): Baseline demographic and clinical parameters. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:1.
 156. Mizokami A, Shigehara K, Sugimoto K, et al. Androgen replacement therapy contributes to improving urinary function in patients with hypogonadism and benign prostate hypertrophy; A randomized, controlled study. *5th Japan-ASEAN Conference on Men's Health and Aging - Defining the Future of Men's Health and Aging Kota Kinabalu, Sabah, Borneo Malaysia. Conference Start: 20100709 Conference End: 20100711. Journal of Men's Health* 2011
 157. Morgentaler A, Sweeney M, Bennett R, et al. PSA and follow-up biopsy results in men who received testosterone therapy while on active surveillance for prostate cancer. *2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA United States. Conference Start: 20100529 Conference End: 20100603. Journal of Urology* 2010;183(4 Suppl 1):e531
 158. Morgentaler A, Wang C, Harnett M. An assessment of the efficacy and safety of intramuscular injections of 750 mg testosterone undecanoate (TU) in hypogonadal men with no history of prior testosterone replacement therapy during a 34 week treatment period. *35th Annual Meeting of the American Society of Andrology, ASA Houston, TX United States. Conference Start: 20100410 Conference End: 20100413. Journal of Andrology* 2010;31:73.
 159. Morgentaler A, Wang C, Harnett M. The efficacy and safety of intramuscular injections of 750mg testosterone undecanoate (TU) in hypogonadal men with no history of prior testosterone replacement therapy in an 84-week treatment period. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine* 2011;8.
 160. Morgentaler, Kaufman JM, Denes BS, et al. Changes in prostate-specific antigen and percent free prostate-specific antigen in men treated with testosterone replacement therapy. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:207
 161. Morrison BF, Reid M, Madden W, et al. Testosterone replacement therapy does not promote priapism in hypogonadal men with sickle cell disease: Twelve month safety report. *21st Annual Research Conference on the Non-Communicable Diseases - A Threat to Life and the Economy Mona Jamaica. Conference Start: 20121107 Conference End: 20121109. West Indian Medical Journal.* 2012;61:2012.
 162. Morrison BF, Reid M, Madden W, et al. Testosterone replacement therapy does not promote priapism in hypogonadal men with sickle cell disease: One year safety monitoring. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:207
 163. Morrison CL, Wong S, Hassanein M, et al. Testosterone deficiency in men with diabetes. *Diabetes UK Professional Conference 2012 Glasgow United Kingdom. Conference Start: 20120307 Conference End: 20120309. Diabetic Medicine.* 2012;29:128.

164. Mskhalaya G, Kalinchenko S, Tishova Y, et al. The Moscow Study: A randomized, placebo-controlled, double-blind trial of parenteral testosterone undecanoate on the prostate status and blood count. *12th European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:523*
165. Mukaddam MA, Rajapakse C, Bhagat Y, et al. Testosterone treatment has differential effects on trabecular and cortical bone strength in men with hypopituitarism. *2012 Annual Meeting of the American Society for Bone and Mineral Research Minneapolis, MN United States. Conference Start: 20121012 Conference End: 20121015. Journal of Bone and Mineral Research 2012;27:201*
166. Muraleedharan V, Dugdale C, Stanworth R, et al. Testosterone replacement may be beneficial in hypogonadal men with cardiovascular disease. *Society for Endocrinology, British Endocrine Societies, BES 2010 Manchester United Kingdom. Conference Start: 20100315 Conference End: 20100318. Endocrine Abstracts 2010;21:176.*
167. Muraleedharan V, Marsh H, Channer KS, et al. Long-term testosterone replacement improves survival in men with type 2 diabetes and hypogonadism. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32(3 Meeting Abstracts).*
168. Namiki M, Koh E, Shigehara K, et al. Testosterone deficiency syndrome. *13th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kaohsiung Taiwan (Republic of China). Conference Start: 20111116 Conference End: 20111120. Journal of Sexual Medicine 2012;9:101-102.*
169. Navarro JF, Mora C, Macia M, et al. Effects of androgen therapy on hematologic and nutritional parameters in elderly peritoneal dialysis patients [abstract]. *International Urology and Nephrology. 2001;33:715*
170. Ni X, Muram D. Effects of baseline testosterone levels on symptom improvement in hypogonadal men receiving testosterone replacement therapy. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:240-241*
171. Ni X, Muram D. Effects of baseline testosterone levels on symptom improvement in hypogonadal men receiving testosterone replacement therapy. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33*
172. Ni X, Muram D. Improvement in sexual function and mood as a function of testosterone level in hypogonadal men receiving testosterone replacement therapy. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:206*
173. Ni X, Muram D. Improvement in sexual function and mood as a function of testosterone level in hypogonadal men receiving testosterone replacement therapy. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33*
174. Park MG, Cho DY, Yeo JK, et al. Exercise improves the effect of testosterone replacement therapy and the durability of response after cessation of treatment. *Journal of Urology. 2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 2014052; 191(4 Suppl 1):e527*
175. Pastuszak A, Badhiwala N, Lipshultz L, et al. The impact of testosterone replacement therapy on lower urinary tract symptoms. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:268*
176. Pastuszak A, Gomez L, Khera M, et al. Comparison of rates and timing of erythrocytosis between testosterone gels, injections and pellets-a single-institution experience. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:285*
177. Pastuszak A, Miles B, Khera M, et al. Testosterone replacement therapy in patients with high risk prostate cancer after radical prostatectomy. *32nd Congress of the Societe Internationale d'Urologie Fukuoka Japan. Conference Start: 20120930 Conference End: 20121004. Urology 2012;80(3 Suppl 1):S97-S98.*
178. Pastuszak A, Morgentaler A, Hulth M, et al. Testosterone therapy after radiation therapy for prostate cancer. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology 2013;189(4 Suppl 1):e624.*
179. Pastuszak AW, Liu J, Lipshultz L, et al. Dose-response and symptomatic improvement using subcutaneous testosterone pellets in hypogonadal men. *16th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America, SMSNA Miami Beach, FL United States. Conference Start: 20101110 Conference End: 20101114. Journal of Sexual Medicine 2011;8.*
180. Pastuszak AW, Liu JS, Lipshultz LI, et al. Pharmacokinetics of testosterone replacement in hypogonadal men treated with subcutaneous testosterone implants. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine 2012;9:48.*
181. Pastuszak AW, Pearlman A, Lipshultz LI, Khera M. Testosterone replacement therapy after radiation therapy for prostate cancer. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine 2012;9:16.*

182. Pastuszak AW, Pearlman A, Sathymoorthy A, et al. Testosterone replacement therapy after radical prostatectomy: Longterm follow-up. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States.Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine* 2012;9:15
183. Pastuszak AW, Pearlman AM, Lipshultz LI, et al. Testosterone replacement therapy after radiation therapy for prostate cancer. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States.Conference Start: 20120519 Conference End: 20120523. Journal of Urology* 2012;187(4 Suppl 1):e603.
184. Pastuszak AW, Pearlman AP, Sathymoorthy K, et al. Testosterone replacement therapy in patients with high risk prostate cancer after radical prostatectomy: Long-term follow-up. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States.Conference Start: 20120519 Conference End: 20120523. Journal of Urology* 2012;187(4 Suppl 1):e603.
185. Pearl J, Berhanu D, Masson P, et al. Testosterone supplementation does not worsen lower urinary tract symptoms. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States.Conference Start: 20130504 Conference End: 20130508. Journal of Urology* 2013;189(4 Suppl 1):e566
186. Permpongkosol S, Ratanaolarn K, Tantiwong A, et al. A prospective, multicenter study on efficacy of long-acting testosterone undecanoate, if desired in combination with vardenafil, in late onset hypogonadal patients with erectile dysfunction. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan.Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine* 2013;10:202
187. Permpongkosol S, Talubsri R. Long-acting intramuscular testosterone undecanoate for the treatment of 118 late-onset hypogonadism in males. *2009 American Urological Association (AUA) Annual Meeting Chicago, IL United States.Conference Start: 20090425 Conference End: 20090430. Journal of Urology* 2009;181(4 Suppl 1):489.
188. Petersson SJ, Frederiksen L, Andersen M, et al. Muscle transcripts of mitochondrial oxidative metabolism genes associate with fuel selection, but do not respond to testosterone therapy in men with subnormal testosterone. *48th Annual Meeting of the European Association for the Study of Diabetes, EASD 2012 Berlin Germany. Conference Start: 20121001 Conference End: 20121005. Diabetologia* 2012;55:S245-S246
189. Petersson SJ, Frederiksen L, Kristensen JM, et al. The effect of androgen therapy on genes and proteins involved in oxidative phosphorylation and lipid metabolism in skeletal muscle of men with subnormal testosterone levels. *73rd Scientific Sessions of the American Diabetes Association Chicago, IL United States. Conference Start: 20130621 Conference End: 20130625. Diabetes* 2013; 62:A312
190. Pope HG, Kanayama G, Cohane GH, et al. Testosterone gel supplementation in treatment refractory depressed men. *155th Annual Meeting of the American Psychiatric Association; May 18-23, Philadelphia, PA. 2002;122*
191. Pourmand G, Sajadi H, Dehghani S, et al. Effects of testosterone administration sexual function in aging males with symptoms of late-onset hypogonadism and normal or subnormal testosterone level: A comparative analysis. *32nd Congress of the Societe Internationale d'Urologie Fukuoka Japan.Conference Start: 20120930 Conference End: 20121004. Urology* 2012;80(3 Suppl 1):S42.
192. Pourmand G, Salem S, Sajadi H, et al. Testosterone administration effects on sexual function in aging males with symptoms of late-onset hypogonadism and normal or subnormal testosterone level: A comparative analysis. *31st Congress of the Societe Internationale d'Urologie, SIU 2011 Berlin Germany.Conference Start: 20111016 Conference End: 20111020 Urology* 2011;78(3 Suppl 1):S358.
193. Pulivarthi K, Dev R, Garcia J, et al. Testosterone replacement for fatigue in male hypogonadic patients with advanced cancer: A preliminary double-blind placebo-controlled trial. *2012 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20120601 Conference End: 20120605. Journal of Clinical Oncology* 2012;30(15 Suppl 1): 2012
194. Ramasamy R, Scovell J, Kovac J, et al. Hypogonadal men taking clomiphene citrate report similar satisfaction compared to men on testosterone replacement therapy. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology* 2014;191(4 Suppl 1):e529.
195. Rao P, Brooke JC, McLaren E, et al. Testosterone therapy improves HbA1c and other cardiovascular risk factors in hypogonadal men with poorly controlled diabetes: A retrospective analysis of five years of clinical practice. *Diabetes UK Professional Conference 2013 Manchester United Kingdom.Conference Start: 20130313 Conference End: 20130315. Diabetic Medicine* 2013;30:146.
196. Raynaud JP, Legros JJ, Rollet J, et al. Efficacy and safety of a new testosterone-inadhesive matrix patch applied every two days for five years to hypogonadal men. *2009 American Urological Association (AUA) Annual Meeting Chicago, IL United States.Conference Start: 20090425 Conference End: 20090430. Journal of Urology* 2009;181(4 Suppl 1):729.
197. Raynaud JP, Legros JJ, Rollet J, et al. Efficacy and safety of a new testosterone in adhesive matrix patch applied every two days for five years to hypogonadal men. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine* 2009;6:128.

198. Rosen RC, Araujo AB, Wu FCW, et al. Sexual and prostate health in a longitudinal, European cohort study: The Registry of Hypogonadism in Men (RHYME). *6th European Congress of Andrology Athens Greece.Conference Start: 20100929 Conference End: 20101001. International Journal of Andrology* 2010;33:62.
199. Rosen RC, Porst H, Maggi M, et al. Testosterone and key aspects of physical and emotional health in untreated hypogonadal men: Baseline findings from the registry of hypogonadism in men (RHYME). *International Symposium on Prostate, Androgens and Men's Sexual Health 2013 Berlin Germany.Conference Start: 20130621 Conference End: 20130623. Journal of Sexual Medicine* 2013;10:257-258.
200. Roth LW, Schwartz RS, Meacham RB. The impact of testosterone supplementation on sexual function in elderly men. *Fertility and Sterility.Conference: 67th Annual Meeting of the American Society for Reproductive Medicine, ASRM 2011 Orlando, FL United States. Conference Start: 20111015 Conference End: 20111019.2011;*96 (3 Suppl 1).
201. Saad A, Haider A, Doros G, et al. Testosterone replacement in 181 obese, hypogonadal men leads to continuous weight loss and over 5 years and improved glucose homeostasis. *49th Annual Meeting of the European Association for the Study of Diabetes, EASD 2013 Barcelona Spain.Conference Start: 20130923 Conference End: 20130927. Diabetologia* 2013;56:S287.
202. Saad A, Haider A, Yassin A. Baseline testosterone levels or age as predictors of favourable effects of normalizing testosterone in men with the metabolic syndrome. *12th Biennial Meeting of the Asia Pacific Society for Sexual Medicine Singapore Singapore.Conference Start: 20091212 Conference End: 20091215. Journal of Sexual Medicine* 2010;47:97-98.
203. Saad A, Haider A. Testosterone administration to elderly hypogonadal men improves the metabolic syndrome, C-reactive protein, and liver steatosis. *10th Biennial Meeting of the Latin American Society for Sexual Medicine Florianopolis Brazil.Conference Start: 20090827 Conference End: 20090830. Journal of Sexual Medicine* 2010;47:66.
204. Saad B, Haider A, Gooren L. Effects of 4 years' testosterone administration on the aging males' symptoms scale and side-effects of long-term treatment. *11th Biennial Congress of the Latin American Society for Sexual Medicine Buenos Aires Argentina.Conference Start: 20110908 Conference End: 20110911. Journal of Sexual Medicine* 2012;9:69.
205. Saad F, Doros G, A Traish, et al. Most hypogonadal men are obese; long-term testosterone treatment leads to continuous reductions of body weight and waist circumference. *5th International Congress on Prediabetes and the Metabolic Syndrome. Early Interventions for Diabetes and Dysglycaemia.Surgery in the Treatment of Obesity and Diabetes Vienna Austria. Conference Start: 20130418. Journal of Diabetes.* 2013.
206. Saad F, Doros G, Haider A, et al. Obese hypogonadal men benefit from long-term testosterone treatment with testosterone undecanoate injections in multiple ways. *International Symposium on Prostate, Androgens and Men's Sexual Health 2013 Berlin Germany.Conference Start: 20130621 Conference End: 20130623. Journal of Sexual Medicine* 2013;10:257-258.
207. Saad F, Doros G, Haider A. Testosterone treatment in elderly hypogonadal men for up to 5 years is efficacious in weight reduction. *World Meeting on Sexual Medicine 2012 Chicago, IL United States.Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:204
208. Saad F, El DY, Yassin A. 4 years testosterone replacement therapy with testosterone undecanoate long acting intramuscular injections is associated with reduction in obesity. *19th European Congress on Obesity, ECO2012 Lyon France.Conference Start: 20120509 Conference End: 20120512. Obesity Facts* 2012;5:183.
209. Saad F, Gooren L, Heufelder A. Testosterone treatment enhances the beneficial effects of lifestyle changes on inflammation and procoagulatory markers in hypogonadal men. *12th Biennial Meeting of the Asia Pacific Society for Sexual Medicine, Singapore.Conference Start: 20091212 Conference End: 20091215. Journal of Sexual Medicine* 2010;47:96.
210. Saad F, Haider A, Doros G, et al. Hypogonadal men completing five years of testosterone treatment progressively lose weight and waist size in a clinically meaningful magnitude. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan.Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine* 2013;10:231
211. Saad F, Haider A, Doros G, et al. Long-term testosterone treatment with testosterone undecanoate injections improves anthropometric measures, inflammation, sexual function and quality of life. *16th Annual Congress of the European Society for Sexual Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey.Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine* 2014.
212. Saad F, Haider A, Doros G, et al. Obese hypogonadal men with type 2 diabetes benefit from long-term treatment with testosterone undecanoate injections. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan.Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine* 2013;10:232
213. Saad F, Haider A, Doros G, et al. Side-effect profile of long-term treatment of elderly hypogonadal men with testosterone undecanoate. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States.Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33(3 Meeting Abstracts).

214. Saad F, Haider A, Doros G, et al. Sustained improvement of features of the metabolic syndrome upon normalization of serum testosterone in hypogonadal men: Follow-up up to 5 years. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3 Meeting Abstracts).*
215. Saad F, Haider A, Doros G, et al. Treatment of patients with a late diagnosis of klinefelter syndrome with testosterone undecanoate for a duration of up to 5 years. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3 Meeting Abstracts).*
216. Saad F, Haider A, Gooren L. Restoring testosterone to normal levels in elderly men is efficacious in weight reduction. A follow-up study over 5 years. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3 Meeting Abstracts).*
217. Saad F, Haider A, Gooren L. Restoring testosterone to normal levels in elderly men is efficacious in weight reduction. A follow-up study over 5 years. *19th European Congress on Obesity, ECO2012 Lyon France. Conference Start: 20120509 Conference End: 20120512. Obesity Facts 2012;5:35-36.*
218. Saad F, Haider A, Yassin A, et al. Continuous improvements of features of the metabolic syndrome over 48 months upon normalization of serum testosterone in three cohorts, in total 410 men. *13th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kaohsiung Taiwan (Republic of China). Conference Start: 20111116 Conference End: 20111120. Journal of Sexual Medicine 2012;9:115.*
219. Saad F, Haider A, Yassin A, et al. Continuous improvements of the metabolic syndrome under testosterone treatment over 48 months in three cohorts, in total 410 men. *9th European Congress on Menopause and Andropause Athens Greece. Conference Start: 20120328 Conference End: 20120331. Maturitas 2012;71:S18.*
220. Saad F, Haider A, Yassin A, et al. Favourable changes in body composition and components of the metabolic syndrome in 410 hypogonadal men receiving testosterone over 48 months. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine 2012;9:15.*
221. Saad F, Haider A, Yassin A, et al. Men with late onset hypogonadism often suffer from other ailments needing treatment and vice versa. *9th European Congress on Menopause and Andropause Athens Greece. Conference Start: 20120328 Conference End: 20120331. Maturitas 2012;71:S18.*
222. Saad F, Haider A, Yassin A, et al. Testosterone administration reduces inflammation and may thus improve lower urinary tract symptoms. *14th World Meeting of the International Society for Sexual Medicine Seoul South Korea. Conference Start: 20100926 Conference End: 20100930. Journal of Sexual Medicine 2010;7:164-165.*
223. Saad F, Haider A, Yassin A, et al. Upon normalization of serum testosterone improvements of features of the metabolic syndrome are continuous over 48 months: A study in three cohorts in total 410 men. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine 2011;8:369*
224. Saad F, Haider A. Testosterone replacement therapy in middle-aged to elderly hypogonadal men leads to continuous weight loss and reduction in waist circumference over five years. *48th Annual Meeting of the European Association for the Study of Diabetes, EASD 2012 Berlin Germany. Conference Start: 20121001 Conference End: 20121005. Diabetologia 2012;55:S366), 2012.*
225. Saad F, Heufelder A, Bunck M, et al. Beneficial effects of testosterone on glucose homeostasis and metabolic syndrome persist after its discontinuation. *14th World Meeting of the International Society for Sexual Medicine Seoul South Korea. Conference Start: 20100926 Conference End: 20100930. Journal of Sexual Medicine 2010;7:183*
226. Saad F, Heufelder A, Bunck M, et al. Fifty-two-week treatment with diet and exercise plus transdermal testosterone improves biomarkers of non-alcoholic fatty liver disease and cardiovascular risk in hypogonadal men with the metabolic syndrome. *12th European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:313*
227. Saad F, Heufelder A, Bunck MC, et al. Beneficial effects of testosterone added to diet and exercise on glycemic control and the metabolic syndrome persist 12 months after discontinuation of testosterone. *4th International Congress on Prediabetes and the Metabolic Syndrome Madrid Spain. Conference Start: 20110406 Conference End: 20110409. Journal of Diabetes 2011;3:268-269*
228. Saad F, Heufelder A, Gooren L. Treatment with diet and exercise plus testosterone reverses the metabolic syndrome and improves glycemic control in hypogonadal men with newly diagnosed type 2 diabetes. *10th Biennial Meeting of the Latin American Society for Sexual Medicine Florianopolis Brazil. Conference Start: 20090827 Conference End: 20090830. Journal of Sexual Medicine 2010;47:52.*
229. Saad F, Kalinchenko S, Tishova Y, et al. Effects of testosterone supplementation on depressive symptoms, Low vitality and sexual dysfunction in hypogonadal men with the metabolic syndrome: The Moscow study. *35th Annual Meeting of the American Society of Andrology, ASA Houston, TX United States. Conference Start: 20100410 Conference End: 20100413. Journal of Andrology 2010;31:73*

230. Saad F, Kalinchenko S, Tishova Y, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: The double-blind placebo-controlled Moscow study. *11th International Congress on Obesity, ICO 2010 Stockholm Sweden. Conference Start: 20100711 Conference End: 20100715. Obesity Reviews 2010;11:48.*
231. Saad F, Kalinchenko S, Tishova Y, et al. Effects on sexual, depressive and ageing male symptoms in hypogonadal men treated with testosterone supplementation: Results from a randomized, placebo-controlled, double-blind trial. *14th World Meeting of the International Society for Sexual Medicine Seoul South Korea. Conference Start: 20100926 Conference End: 20100930. Journal of Sexual Medicine 2010;7:164*
232. Saad F, Kalinchenko S, Tishova Y, et al. Long-term effects of normalization of testosterone on variables of the metabolic syndrome in hypogonadal men. *18th European Congress on Obesity, ECO 2011 Istanbul Turkey. Conference Start: 20110525 Conference End: 20110528. Obesity Reviews 2011;12:203*
233. Saad F, Nasser M, Doros G, et al. Hypogonadal patients with Crohn's disease benefit from treatment with testosterone data from an ongoing, long-term, observational registry study. *9th Congress of the European Crohn's and Colitis Organisation, ECCO 2014 Copenhagen Denmark. Conference Start: 20140220 Conference End: 20140222. Journal of Crohn's and Colitis 2014;8:S260-S261*
234. Saad F, Tishova Y, Mskhalaya G, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: The placebo-controlled Moscow study. *35th Annual Meeting of the American Society of Andrology, ASA Houston, TX United States. Conference Start: 20100410 Conference End: 20100413. Journal of Andrology 2010;31:73*
235. Saad F, Traish A, Doros G, et al. Profound weight loss in 159 obese hypogonadal men treated with injectable testosterone undecanoate for up to five years. *20th European Congress on Obesity, ECO 2013 Liverpool United Kingdom. Conference Start: 20130512 Conference End: 20130515. Obesity Facts 2013;6:124-125.*
236. Saad F, Yassin A, Doros G, et al. 162 hypogonadal men with obesity respond to long-term treatment with testosterone undecanoate with unexpected weight loss. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan. Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine 2013;10:232*
237. Saad F, Zitzmann M, Kliesch S, et al. Beneficial effects on all metabolic syndrome components after treatment with testosterone undecanoate injections for up to 15 years in 334 hypogonadal men. *5th International Congress on Prediabetes and the Metabolic Syndrome. Early Interventions for Diabetes and Dysglycaemia. Surgery in the Treatment of Obesity and Diabetes Vienna Austria. Conference Start: 20130418. Journal of Diabetes. 2013.*
238. Saad F, Zitzmann M, Kliesch S, et al. Weight, waist circumference and all other metabolic syndrome components improve after long-term testosterone treatment in 334 hypogonadal men. *20th European Congress on Obesity, ECO 2013 Liverpool United Kingdom. Conference Start: 20130512 Conference End: 20130515. Obesity Facts 2013;6:122.*
239. Saad F. Testosterone and obesity-an intimate partnership. *11th Asian Congress of Urology of the Urological Association of Asia, ACU 2012 Pattaya Thailand. Conference Start: 20120822 Conference End: 20120826. International Journal of Urology 2012;19:51.*
240. Saad F.. Age and baseline testosterone value do not predict the beneficial effect of normalization of testosterone on the metabolic syndrome..Conference: *8th European Congress on Menopause, EMAS London United Kingdom. Conference Start: 20090516 Conference End: 20090520 Maturitas 2009;63:S32-S33.*
241. Saad G, Doros G, Haider A. Side effect profile of long-term treatment of elderly hypogonadal men with testosterone undecanoate. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:251*
242. Saad, A. Haider, W. Kurtz, M. Nasser, L. Gooren. Long-term testosterone treatment with injectable testosterone undecanoate in hypogonadal men with inflammatory bowel diseases (M. Crohn and colitis ulcerosa). *Endocrine Reviews. Conference: 94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Conference Publication: (var.pagings).33 (3 Meeting Abstracts) , 2012. Date of. 2012///. #volume#: #pages#*
243. Sand A, Mocclair B, Hemani M, et al. A phase IV prospective evaluation of extended release testosterone pellets: Dose-response patterns and the effect of increasing BMI. *20th World Congress of Sexual Health Glasgow United Kingdom. Conference Start: 20110612 Conference End: 20110616. Journal of Sexual Medicine 2011;8:183.*
244. Sand A, Mocclair B, Hemani M, et al. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for treatment of male hypogonadism. *20th World Congress of Sexual Health Glasgow United Kingdom. Conference Start: 20110612 Conference End: 20110616. Journal of Sexual Medicine 2011;8:183.*
245. Sand B, Mocclair B, Kaminetsky J. A phase IV prospective evaluation of extended release testosterone pellets: Dosage guidelines and the effect of increasing BMI. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine 2012;9:18.*
246. Sand M, Hemani M, Mocclair B, Kaminetsky J. A phase IV prospective evaluation of extended release testosterone pellets: Dose-response patterns and the effect of increasing BMI. *2011 Annual Meeting of the American Urological*

- Association, AUA Washington, DC United States. Conference Start: 20110514 Conference End: 20110519. *Journal of Urology*. 2011;185(4 Suppl 1):e672.
247. Sand M, Moclair B, Kaminetsky J. Long term follow-up of patients from a prospective, phase IV clinical trial of extended release testosterone pellets: An assessment of patient compliance. *17th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America Las Vegas, NV United States. Conference Start: 20111110 Conference End: 20111113. Journal of Sexual Medicine* 2012;9:17
 248. Sante S., Connors WP, Flinn K, et al. Influence of baseline testosterone levels on body composition changes with testosterone therapy. *2011 Annual Meeting of the American Urological Association, AUA Washington, DC United States. Conference Start: 20110514 Conference End: 20110519. Journal of Urology*. 2011;185(4 Suppl 1):e673.
 249. Sathyaamoorthy K, Mohamed O, Stein M, et al. Follow-up series of testosterone replacement therapy following radical prostatectomy: The Baylor experience. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:1.
 250. Sathyaamoorthy K, Stein M, Mohamed O, et al. Testosterone replacement therapy in high risk patients following radical prostatectomy. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:4
 251. Sathyaamoorthy K, Stein M, Mohamed O, et al. The risk of erythrocytosis with testosterone gel therapy. *15th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America San Diego, CA United States. Conference Start: 20091119 Conference End: 20091121. Journal of Sexual Medicine* 2010;47:3.
 252. Sathyaamoorthy K, Stein M, Mohammed O, et al. Testosterone replacement therapy in high risk patients following radical prostatectomy. *2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA United States. Conference Start: 20100529 Conference End: 20100603. Journal of Urology* 2010;183(4 Suppl 1):e577
 253. Schmidt SL, Kealey EH, Horton TJ, et al. Effects of testosterone on fat metabolism in young healthy males. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews* 2012;33
 254. Schoenfeld MJ, Shortridge E, Cui, Z, et al. Medication adherence and persistence for hypogonadal patients treated with topical testosterone therapy: A retrospective claims analysis. *17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Value in Health* 2012;A206
 255. Schoenfeld MJ, Shortridge EF, Cui Z, et al. Medication adherence and persistence for hypogonadal patients treated with topical testosterone therapy: A retrospective claims analysis. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:239
 256. Schoenfeld MJ, Shortridge EF, Cui Z, et al. Topical testosterone gel treatment patterns among hypogonadal men in a large retrospective claims database. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:240
 257. Seidman S, Amiaz R, Pope H, et al. Exogenous testosterone for male depression: Recent clinical trials. *5th International Congress on Gender Medicine Tel Aviv Israel. Conference Start: 20101130 Conference End: 20101203. Gender Medicine* 2010;7(5):493
 258. Seidman S, Pope H, Amiaz R, et al. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: A randomized, placebo-controlled clinical trial. *5th International Congress on Gender Medicine Tel Aviv Israel. Conference Start: 20101130 Conference End: 20101203; Gender Medicine* 2010;7(5):529.
 259. Seidman SN, Roose SP. Testosterone replacement for male depression: Randomized clinical trial. *153rd Annual Meeting of the American Psychiatric Association, 2000 May 13-18, Chicago, IL. 2000;NR111*
 260. Seidman SN, Roose SP. Testosterone replacement for male depression: randomized clinical trial. *155th Annual Meeting of the American Psychiatric Association; 2002 May 18-23rd; Philadelphia, PA. 2002.*
 261. Shin H, Cho H, Park J, et al. The effect of testosterone replacement therapy in men with testosterone deficiency syndrome on cognitive function and depression. *32nd Congress of the Societe Internationale d'Urologie Fukuoka Japan. Conference Start: 20120930 Conference End: 20121004. Urology* 2012;80(3 Suppl 1): S311-S312
 262. Shin HS, Park JS, Moon KH et al. The effect of testosterone replacement in men with testosterone deficiency syndrome on cognitive performance and depression. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine* 2012;9:238
 263. Shin HS, Park JS, Moon KH, et al. The influence of lower urinary tract symptoms during testosterone replacement therapy in men with testosterone deficiency syndrome. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine* 2011;8:432.
 264. Shores M, Kivlahan D, Matsumoto A. Incident depression in hypogonadal men treated with testosterone. *AAGP Annual Meeting 2009 Honolulu, HI United States. Conference Start: 20090305 Conference End: 20090308. American Journal of Geriatric Psychiatry American Journal of Geriatric Psychiatry* 2009;17:A52.

265. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment is associated with reduced mortality in men with low serum testosterone levels. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32(3 Meeting Abstracts).*
266. Shortridge E, Lanes S, Polzer P, et al. Diagnosis and treatment patterns in the clinical practice research datalink (CPRD): A population study of men with hypogonadism with and without type 2 diabetes who initiated treatment with testosterone replacement therapy. *16th Annual Congress of the European Society for Sexual Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey. Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine 2014.*
267. Snabes MC, Berry S, Zborowski J, et al. Libigel (Testosterone gel) Safety study enters fourth year with a continued low rate of cardiovascular and breast cancer events. *Journal of Sexual Medicine. 2011;8:125.*
268. Snajderova M, El BK, Sobotka V, et al. Hormone replacement therapy in young men with hypogonadism: Quality of life according IPSS, ams and iief scores. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3 Meeting Abstracts).*
269. Solomon LR, Hendler ED. Androgen therapy in hemodialysis patients: effects on red cell metabolism and exercise tolerance [abstract: 10]. *Blood. 1986;68:58a.*
270. Sommer F, Mathers MJ. A conservative approach to penile enlargement: A prospective, placebocontrolled parallel-group trial. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:226*
271. Spitzer MJ, Basaria S, Davda MD, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: A randomized, placebo-controlled trial. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33*
272. Stanworth R, Jones TH. Testosterone replacement therapy has no effect on ultrasound assessed carotid artery stiffness and intima-media thickness in men with insulin treated type 2 diabetes. *Society for Endocrinology, British Endocrine Societies, BES 2010 Manchester United Kingdom. Conference Start: 20100315 Conference End: 20100318. Endocrine Abstracts 2010;21:135.*
273. Stanworth RD, Akhtar S, Channer KS, et al. Androgen receptor CAG repeat polymorphism modulates change in triglycerides, diastolic blood pressure and PSA during testosterone replacement therapy in men with metabolic syndrome or type 2 diabetes - The TIMES2 study. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32*
274. Stout M, Doll H, Woodroffe N, et al. Cardiovascular effects of testosterone and exercise training in hypogonadal males with chronic heart failure. *Heart Failure Congress 2011 Gothenburg Sweden. Conference Start: 20110521 Conference End: 20110524. European Journal of Heart Failure 2011;10:S34*
275. Suarez S, Costanzo P, Knoblovits P, et al. Prostate-specific antigen values in men with late-onset hypogonadism under testosterone replacement treatment. *10th Biennial Meeting of the Latin American Society for Sexual Medicine Florianopolis Brazil. Conference Start: 20090827 Conference End: 20090830. Journal of Sexual Medicine 2010;47: 58*
276. Suetomi T, Oikawa T, Johraku A, et al. Effect of intramuscular testosterone replacement on bone status in Japanese men with late-onset hypogonadism. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan. Conference Start: 20130531 Conference End: 20130602. Journal of Sexual Medicine 2013;10:231*
277. Suetomi T, Oikawa T, Kojima T, et al. Effect of intramuscular testosterone replacement on insulin resistance in Japanese men with late-onset hypogonadism. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:282*
278. Szmulewitz RZ, Posadas EM, Manchen B, et al. A randomized, double-blind, placebo-controlled phase II study of testosterone replacement in men with asymptomatic castrate-resistant prostate cancer (PC). *2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. Conference Start: 20100604 Conference End: 20100608. Journal of Clinical Oncology 2010;28(15 Suppl 1)*
279. Tan HM, Tong SF, Low WY, et al. The effect of long-acting testosterone treatment on the Aging Male Symptoms (AMS) scale - A randomized double blind placebocontrol trial. *26th Annual Congress of the European Association of Urology, EAU Vienna Austria. Conference Start: 20110318 Conference End: 20110322. European Urology 2011;10:129*
280. Taylor FL, Levine LA. Clomiphene citrate versus testosterone gel replacement therapy for hypogonadism: Biochemical and clinical efficacy and treatment cost. *2009 American Urological Association (AUA) Annual Meeting Chicago, IL United States. Conference Start: 20090425 Conference End: 20090430. Journal of Urology 2009;181(4 Suppl 1):488.*
281. Tishova Y, Kalinchenko S, Mskhalaya G, et al. The Moscow study: A randomized, placebo-controlled, double-blind trial of parenteral testosterone undecanoate on the metabolic syndrome components and body composition. *12th*

- European Congress of Endocrinology 2010, ECE 2010 Prague Czech Republic. Conference Start: 20100424 Conference End: 20100428. Endocrine Abstracts 2010;22:681.*
282. Tishova Y, Kalinchenko S, Novikova M, et al. Chronic renal disease, hyperfiltration, metabolic syndrome and hypogonadism: Is there a link? *11th European Congress of Endocrinology, ECE 2009 Istanbul Turkey. Conference Start: 20090425 Conference End: 20090429. Endocrine Abstracts 2010;20:457.*
 283. Tolra J, Rodriguez J.M, Cuadrado Campana, Barreda J, Torremade, Knecht E, Llorens De, Miranda E, Franco. Effects on cardiovascular risks and safety of 12 months of treatment with 50 mg testosterone gel followed by 12 months testosterone undecanoate in men with late-onset hypogonadism. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine 2011;8:431.*
 284. Tolra J, Rodriguez J.M, Cuadrado Campana, Barreda J, Torremade, Knecht E, Llorens De, Miranda E, Franco. Increases in bone mineral density and lean body mass in men with late-onset hypogonadism upon 12 months of treatment with 50 mg testosterone gel followed by 12 months testosterone undecanoate. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine 2011;8:431.*
 285. Tong SF, Ng CN, Lee BC, et al. Effect of long-acting testosterone treatment on men's quality of life: A double blind randomised control trial. *ISMH World Congress 2010 Nice France. Conference Start: 20101028 Conference End: 20101030. Journal of Men's Health 2010;7(3):323.*
 286. Travison TG, Basaria S, Storer TW, et al. The effects of testosterone on muscle performance and physical function in older men with mobility limitation. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32*
 287. Tsai WK, Hwang TIS, Wu HC, et al. Effect and safety of long-term androgen replacement for hypogonadism in Taiwan. *14th Biennial Meeting of the Asia-Pacific Society for Sexual Medicine Kanazawa Japan. Conference Start: 20130531 Conference End: 20130602 Journal of Sexual Medicine 2013;10:188.*
 288. Uryadnova M, Kalinchenko S, Tishova T, et al. Is testosterone therapy safe for cardiovascular system? The impact of cardiac ultrasound monitoring. *11th European Congress of Endocrinology, ECE 2009 Istanbul Turkey. Conference Start: 20090425 Conference End: 20090429. Endocrine Abstracts 2010;20:407.*
 289. Vertkin AL, Morgunov LY, Naumov AV, et al. Effectiveness and safety of testosterone replacement therapy in males with somatic pathology. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine 2009;6:168.*
 290. Vigen R, Barqawi A, Maddox TM, et al. The association between testosterone replacement therapy and adverse cardiovascular outcomes in veterans undergoing coronary angiography. *American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium Los Angeles, CA United States. Conference Start: 20121103 Conference End: 20121106. Circulation 2012;126 (21 Suppl 1)*
 291. Virag R, Sussman H, Costa C. Very long-term outcome of a cohort of 542 ED patients under self-intracavernous injections. *14th Annual Congress of the European Society for Sexual Medicine Milan Italy. Conference Start: 20111201 Conference End: 20111204. Journal of Sexual Medicine 2011;8:372*
 292. Wagner A, Prenner G, Dobnig H, et al. Testosterone replacement on top of bisphosphonate therapy has an additional benefit on bone mass, libido and sexual activity in male cardiac transplant patients: A 5-year prospective controlled study. *94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012 Houston, TX United States. Conference Start: 20120623 Conference End: 20120626. Endocrine Reviews 2012;33(3).*
 293. Wiehle RD, Rosner M, Wike J, et al. The pharmacodynamics and pharmacokinetics of enclomiphene citrate in men with secondary hypogonadism shows restoration of normal HPA function. *World Meeting on Sexual Medicine 2012 Chicago, IL United States. Conference Start: 20120826 Conference End: 20120830. Journal of Sexual Medicine 2012;9:296-297*
 294. Winter A, Marte A, Kelly M, et al. Predictors of poor response to transdermal testosterone therapy in men with metabolic syndrome. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e528.*
 295. Wyllie MG, Dinsmore WW. Striant: Pharmacokinetics, tolerability and safety in Hypogonadal males. *20th World Congress of Sexual Health Glasgow United Kingdom. Conference Start: 20110612 Conference End: 20110616. Journal of Sexual Medicine 2011;8:190*
 296. Wynia B, Lee T, Taneja S, et al. Testosterone replacement therapy in patients with prostate cancer after prostatectomy: A 5-year single center experience. *Journal of Urology. 2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521; 191(4 Suppl 1):pp e527-e528.*
 297. Yassin A, Douaihy Y, Yassin ADJ, et al. Long term testosterone treatment improves all metabolic syndrome domains. *64th Kongresses der Deutschen Gesellschaft für Urologie Leipzig Germany. Conference Start: 20120926 Conference End: 20120929. Urologe - Ausgabe A 2012;51:115.*

298. Yassin A, Douaihy Y, Yassin DJ, et al. Testosterone replacement therapy with testosterone undecanoate long acting intramuscular injections is associated with reduction in obesity. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States. Conference Start: 20120519 Conference End: 20120523. Journal of Urology 2012;187(4 Suppl 1):e466.*
299. Yassin A, Haider A, Saad F. Combination therapy for erectile dysfunction with testosterone and vardenafil in hypogonadal patients who failed to respond to testosterone treatment alone. *62th Kongresses der Deutschen Gesellschaft für Urologie Dusseldorf Germany. Conference Start: 20100922 Conference End: 20100925. Urologe 2010;49:91*
300. Yassin A, Traish A, Doros G, et al. 162 hypogonadal men with obesity respond to long-term treatment with testosterone undecanoate with unexpected weight loss. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e336.*
301. Yassin A, Yassin ADJ, Haider A. Restoring erectile function in hypogonadal elderly patients who failed to respond to testosterone treatment alone, upon combination with Vardenafil. *2011 Annual Meeting of the American Urological Association, AUA Washington, DC United States. Conference Start: 20110514 Conference End: 20110519. Journal of Urology 2011;185(4 Suppl 1):e672*
302. Yassin A, Yassin DJ, Traish A, et al. Long-term testosterone treatment leads to progressive weight loss and waist size reduction in hypogonadal men. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e527.*
303. Yassin AA, Haider A, Shamsodini A, et al. Exogenous testosterone therapy and testicular volume - Is there an alteration? *10th Congress of the European Federation of Sexology. Sexology Past, Present and Future: Celebrating a Century of the Multidisciplinary Science of Sex, EFS 2010 Porto Portugal. Conference Start: 20100509 Conference End: 20100513. Sexologies 2010.*
304. Yassin AA, Saad F. Combination therapy of erectile dysfunction with testosterone and Vardenafil in hypogonadal patients who failed to respond to TT alone. *10th Congress of the European Federation of Sexology. Sexology Past, Present and Future: Celebrating a Century of the Multidisciplinary Science of Sex, EFS 2010 Porto Portugal. Conference Start: 20100509 Conference End: 20100513. Sexologies 2010*
305. Yassin AA, Saad F. Long-acting testosterone ester injection as a first line therapy in hypogonadal patients with erectile dysfunction. *10th Congress of the European Federation of Sexology. Sexology Past, Present and Future: Celebrating a Century of the Multidisciplinary Science of Sex, EFS 2010 Porto Portugal. Conference Start: 20100509 Conference End: 20100513. Sexologies 2010.*
306. Yassin AA, Shamsodini A, Saad F. There is no increase of prostate cancer cases on exogenous testosterone treatment in patients with late onset hypogonadism. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine 2009;6:58*
307. Yassin AA, Yassin ADJ, Haider A, et al. Prostate health & safety parameters: Hypogonadal patients on TRT are not at higher risk than eugonadal subjects of age-matched control group-prospective comparative 6-year fu analysis. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32(3 Meeting Abstracts).*
308. Yassin AA, Yassin ADJ, Haider A, et al. Testosterone treatment in elderly hypogonadal patients does not increase prostate cancer risk: Prospective comparative 6-year follow-up analysis with age-matched controls. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32(3 Meeting Abstracts).*
309. Yassin ADJ, El DY, Gosh P, et al. Waist circumference is superior to weight and BMI in predicting sexual symptoms, voiding symptoms and psychosomatic symptoms in men with late onset hypogonadism. *27th Annual Congress of the European Association of Urology, EAU Paris France. Conference Start: 20120224 Conference End: 20120228. European Urology 2012;11(1):e589.*
310. Yassin DJ, Haider A, Zitzmann M, et al. Effects of long-term treatment with testosterone undecanoate injections in hypogonadal men on waist circumference, body weight and BMI. *28th Annual Congress of the European Association of Urology, EAU Milan Italy. Conference Start: 20130315 Conference End: 20130319. European Urology 2013;12(1):e207.*
311. Yassin DJ, Haider A, Zitzmann M, et al. Effects of long-term treatment with testosterone undecanoate injections in hypogonadal men on waist circumference, body weight and BMI. *2013 Annual Meeting of the American Urological Association, AUA San Diego, CA United States. Conference Start: 20130504 Conference End: 20130508. Journal of Urology 2013;189(4 Suppl 1):e573.*
312. Yassin DJ, Yassin A, Hammerer P. Completing five years of testosterone treatment leads to progressive weight loss and waist size reduction as well as improvement of metabolic syndrome parameters in men with late onset hypogonadism (LOH). *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e334*

313. Yassin DJ, Yassin A, Hammerer P. Testosterone replacement therapy improves the quality of life of hypogonadal men diagnosed with "late onset hypogonadism" Assessed by validated questionnaires. *2014 Annual Meeting of the American Urological Association, AUA Orlando, FL United States. Conference Start: 20140516 Conference End: 20140521. Journal of Urology 2014;191(4 Suppl 1):e336*
314. Yassin DJ, Yassin A, Saad F, et al. Testosterone treatment in elderly hypogonadal patients does not increase prostate cancer risk: Results of a prospective comparative study. 7 years follow up analysis to age-matched controls. *2012 Annual Meeting of the American Urological Association, AUA Atlanta, GA United States. Conference Start: 20120519 Conference End: 20120523. Journal of Urology 2012;187(4 Suppl 1):e152.*
315. Zahran AR, Hussein T, Husse T. Hypogonadism prevalence among patients presenting with metabolic syndrome: An initial experience with testosterone treatment. *Joint Meeting of the European (ESSM) and International (ISSM) Societies for Sexual Medicine Brussels Belgium. Conference Start: 20081207 Conference End: 20081211. Journal of Sexual Medicine. 2009;6:78*
316. Zhang E, Zhang B, Chen J, et al. Sildenafil plus undecanoate and sildenafil alone in the treatment of type 2 diabetic patients with erectile dysfunction. *23rd Great Wall International Congress of Cardiology, Asia Pacific Heart Congress 2012 Beijing China. Conference Start: 20121011 Conference End: 20121014. Heart 2012;98:E154-E155*
317. Zitzmann M, Hanisch J, Mattern A, et al. Prostate safety and effectiveness of testosterone replacement therapy in male hypogonadism: Final results from the largest international trial involving 1493 patients. *26th Annual Congress of the European Association of Urology, EAU Vienna Austria. Conference Start: 20110318 Conference End: 20110322. European Urology 2011;10:130*
318. Zitzmann M, Hanisch JU, Mattern A, et al. Prostate safety of testosterone replacement therapy in male hypogonadism: Interim Results from the largest international trial on injectable long-acting testosterone undecanoate involving 763 patients. *25th Anniversary Congress of the European Association of Urology, EAU Barcelona Spain. Conference Start: 20100416 Conference End: 20100420. European Urology 2010;9(2):56-57.*
319. Zitzmann M, Hanisch JU, Mattern A, et al. Testosterone replacement therapy in male hypogonadism: Final results from the largest international substitution trial involving 1493 patients. *93rd Annual Meeting and Expo of the Endocrine Society, ENDO 2011 Boston, MA United States. Conference Start: 20110604 Conference End: 20110607. Endocrine Reviews 2011;32*
320. Zitzmann M, Saad F, Kliesch S, et al. Weight loss and beneficial effects on the metabolic syndrome as a result of testosterone treatment for up to 16 years in 381 hypogonadal men. *49th Annual Meeting of the European Association for the Study of Diabetes, EASD 2013 Barcelona Spain. Conference Start: 20130923 Conference End: 20130927. Diabetologia 2013;56:S287-S288.*
321. Zitzmann M, Saad F, Kliesch S. Long-term treatment with testosterone undecanoate injections leads to sustained weight loss and improvement of metabolic syndrome parameters in 381 hypogonadal men. *16th Annual Congress of the European Society for Sexual Medicine and the 12th Congress of the European Sexology Federation Istanbul Turkey. Conference Start: 20140129 Conference End: 20140201. Journal of Sexual Medicine 2014.*

APPENDIX 5: RISK OF BIAS ASSESSMENT OF RANDOMIZED CONTROLLED TRIALS

Hackett 2013	Judgment	Quote	Comment
Sequence generation	Unclear	"The study medication was prepared by the manufacturing company of TU ... and randomised in blocks according to the standard processes used throughout the drug development programme." "Randomisation of patients by sequential numbered blocks ..." "Randomisation orders were determined by the manufacturer according to standard procedures applied to all the licensing studies for the drug."	The "standard process" is not described. Not enough information to make a judgment
Allocation concealment	Low	"Identification of the trial medication was by numbered sealed packages, and each subject was assigned to the next lowest numbered sealed package. The code breaks were retained by the study statisticians until the last patient completed the study and the codes were not broken until the last study procedure was carried out and data bases were locked."	Randomization assigned by numbered sealed packages
Blinding (objective outcomes)	Low	"double-blind placebo-controlled study..." "Identification of the trial medication was by numbered sealed packages, and each subject was assigned to the next lowest numbered sealed package." "The code was retained by the study statisticians until the last patient completed the study and the codes were not broken until the last study procedure was carried out and data bases were locked. The placebo was an analogue of the same appearance, but without any active substance, containing the vehicle castor oil and benzyl benzoate."	Description of blinding sufficient
Blinding (subjective outcomes)	Low	"... double-blind placebo-controlled study..." "Identification of the trial medication was by numbered sealed packages, and each subject was assigned to the next lowest numbered sealed package." "The code was retained by the study statisticians until the last patient completed the study and the codes were not broken until the last study procedure was carried out and data bases were locked. The placebo was an analogue of the same appearance, but without any active substance, containing the vehicle castor oil and benzyl benzoate."	Description of blinding sufficient
Incomplete data (efficacy outcomes)	Low	A total of 211 patients were screened with 199 entering the double-blind phase and 190 completing 30 weeks of placebo controlled intervention..."	Completion rate: Placebo: 95/102 (93%) TU: 91/97 (94%)
Incomplete data (safety outcomes)	Low	"Of the nine withdrawals, four were in the active group and five with placebo. There were four serious AEs: one in each group developed bowel malignancies felt to be unrelated to treatment, with a death on placebo due to postoperative septicemia following elective knee replacement and a further placebo patient developing prostate cancer without rise in PSA, diagnosed by digital rectal examination (DRE) after the patient reported worsening urinary symptoms at medical assessment. Of the five who withdrew consent, only one, on placebo, gave a medical reason, which was injection-related pain."	Safety well reported
Wang 2013	Judgment	Quote	Comment
Sequence generation	Unclear	"A total of 186 elderly male osteoporosis patients with low serum testosterone were randomized into three groups: low-dose TU (20 mg, per day), standard-dose TU (40 mg, per day), and placebo group with a 24-month follow up."	Sequence generation not reported
Allocation concealment	Unclear	Not reported	Allocation concealment not reported
Blinding	Low	"This study was designed as a 2-year single-centre, randomized,	Open-label clinical trial;

Hackett 2013	Judgment	Quote	Comment
(objective outcomes)		placebo-controlled, open-label clinical trial."	however, the risk of bias is judged as low for objective outcomes
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Low	"The numbers of withdrawals were similar in the three groups (five, four, and four men in groups A, B, and C). Dropouts were due to lack of compliance to the treatment in these patients." Completed: Group A: 57/62 = 92% Group B: 58/62 = 94% Group C: 58/62 = 94%	Completion rate > 80% in each group
Incomplete data (safety outcomes)	High	"Throughout the 2-years observation, both doses of [TU] were equally well tolerated and their safety profile was similar to that of placebo." "The numbers of withdrawals were similar in the three groups (five, four, and four men in groups A, B, and C). Dropouts were due to lack of compliance to the treatment in these patients."	No further data was available regarding the numbers and types cases of adverse events per group.
Shabsigh 2004	Judgment	Quote	Comment
Sequence generation	Low	"Randomization was based on a computer generated schedule stratified by investigator."	Computer-generated randomization
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"A randomized, placebo controlled, double-blind, parallel group, multicenter study was performed." "Containers of study gel were identical in appearance and construction."	Blinding method is sufficient to result in a low risk of bias
Blinding (subjective outcomes)	Low	"A randomized, placebo controlled, double-blind, parallel group, multicenter study was performed." "Containers of study gel were identical in appearance and construction."	Description of blinding sufficient
Incomplete data (efficacy outcomes)	Low	"Efficacy analyses were conducted on an intent-to-treat (ITT) basis with last observations carried forward. The efficacy population was defined as subjects who received at least 1 dose of study gel and had at least 1 post-baseline efficacy assessment."	Completion: Overall: 63/75 = 84% Placebo: 31/36 = 86% Androgl: 32/39 = 82% Judged low risk because completion was > 80 % and analysis was ITT. Handling of missing data was not judged to be adequate (LOCF), but the rates were similar between groups
Incomplete data (safety outcomes)	Unclear	All withdrawals were accounted for: Lost to follow: P 2, T 3 Withdrew consent: P 2, T 1 Adverse Event: P 0, T 1 Investigator decision: PL 0, T 1 Other: P 1, T 1	Completion as above, and all withdrawals were accounted for; however, type of adverse event and "other" not described
Borst 2014	Judgment	Quote	Comment
Sequence generation	Low	"A randomization table was prepared with RanPro release 1.1 (Applied Logic Associates, Houston, TX) ..."	Unable to locate the method of randomization as cited in the paper, but likely that randomization was done via computer-based program
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective)	Low	"Study participants and investigators performing consenting, screening, drug administration, safety testing, and outcomes	Authors reported the use of matching placebo pills and

Hackett 2013	Judgment	Quote	Comment
outcomes)		testing were blinded to treatment. The only unblinded team members were Research Pharmacy, the Laboratory Manager, who compared safety testing values to removal criteria, and the Study Physician, who assessed adverse events to determine removal criteria."	matching vehicle for those receiving intramuscular injection
Blinding (subjective outcomes)	High	"Study participants and investigators performing consenting, screening, drug administration, safety testing, and outcomes testing were blinded to treatment. The only unblinded team members were Research Pharmacy, the Laboratory Manager, who compared safety testing values to removal criteria, and the Study Physician, who assessed adverse events to determine removal criteria."	Outcome assessment was unblinded
Incomplete data (efficacy outcomes)	High	Completion overall: 40/60 (66.7%) Testosterone IM: 7/14 (50%) Placebo: 12/16 (75%) Combination: 13/17 (76.5%)* Finasteride: 8/13 (61.5%)* "40 participants completed 12 months of treatment. 9 participants dropped out for personal reasons, 5 were removed for adverse events unrelated to treatment, and 6 for adverse events that were probably related to treatment." "Missing at random was presumed for our analyses, and we chose not to use imputation, because it results in greater bias"	High rate of discontinuation. Discontinuation was high and variable across groups, with little detail provided as to whether intention to treat population was used in the analysis. *Data from combination and finasteride groups not used in analysis
Incomplete data (safety outcomes)	High	"40 participants completed 12 months of treatment. 9 participants dropped out for personal reasons, 5 were removed for adverse events unrelated to treatment, and 6 for adverse events that were probably related to treatment."	Little detail provided about the reasons for discontinuations
Stout 2012	Judgment	Quote	Comment
Sequence generation	Unclear	"Blocked randomisation by a third party, using a pre-determined randomisation schedule"	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	NA	NA	No objective outcomes of interest
Blinding (subjective outcomes)	Low	"Members of the research team responsible for assessment of the primary and secondary outcomes and for delivering the supervised exercise training will be blinded to group allocation" "Patients will be blinded to the identity of the injection and the drug will be drawn up away from the patient."	Blinding sufficiently described
Incomplete data (efficacy outcomes)	High	"Five patients dropped out from ET [exercise with testosterone] (25%) and 7 from EP [exercise with placebo] (35%), giving an overall attrition of 30%. The clinical characteristics of the patients who dropped out were similar to the completers, with the exceptions of age (71.6 ± 8.1 years) and functional fitness (ISWT = 336 ± 171 m). Comorbidities accounted for most of the attrition, and there were no study-related adverse events."	Withdrawal rate 30% and not well described for each group. Reasons for withdrawals were provided for each participant; however, to which group they belonged to was not provided
Incomplete data (safety outcomes)	High	As above	Authors reported only treatment-related adverse events, and they did not consider adverse events such as infection and atrial fibrillation as being relevant.
Spitzer 2012	Judgment	Quote	Comment
Sequence generation	Unclear	"Participants were randomly assigned without stratification in a concealed 1:1 allocation to either testosterone or placebo gel by using permuted blocks with a block size of 4. A statistician generated a randomization sequence, which was given to the investigational drug pharmacy for implementation."	Sequence generation not described in sufficient detail

Hackett 2013	Judgment	Quote	Comment
Allocation concealment	Low	"Pharmacists assigned participants to a randomization number and testosterone or placebo gel and recorded allocation in a concealed table."	Judged low risk because allocation was pharmacy controlled
Blinding (objective outcomes)	Low	"The investigating staff and participants were blinded to intervention allocation. Testosterone and placebo gels were packaged in identical tubes, and participants were prescribed 3 tubes of gel daily to maintain blinding. Investigators and study staff did not have access to the randomization table, which was sequestered by the pharmacist." "Participants were instructed to apply 3 tubes of gel daily to facilitate dosing of testosterone at 5, 10, or 15 g daily while maintaining blinding. Men in the testosterone group initially received 2 active tubes, each containing 5 g of testosterone gel, and 1 tube of placebo gel, whereas men in the placebo group received 3 tubes of placebo gel. Two weeks after randomization, testosterone levels were measured and reviewed by an unblinded physician, who increased the daily testosterone dose to 15 g (3 active tubes) if the mean testosterone level was less than 17.35 nmol/L (500 ng/dL) or decreased it to 5 g (1 active tube plus 2 tubes of placebo gel) if the mean testosterone level was greater than 34.7 nmol/L (1000 ng/dL).	Blinding sufficiently described
Blinding (subjective outcomes)	Low	"The investigating staff and participants were blinded to intervention allocation. Testosterone and placebo gels were packaged in identical tubes, and participants were prescribed 3 tubes of gel daily to maintain blinding. Investigators and study staff did not have access to the randomization table, which was sequestered by the pharmacist." "Participants were instructed to apply 3 tubes of gel daily to facilitate dosing of testosterone at 5, 10, or 15 g daily while maintaining blinding. Men in the testosterone group initially received 2 active tubes, each containing 5 g of testosterone gel, and 1 tube of placebo gel, whereas men in the placebo group received 3 tubes of placebo gel. Two weeks after randomization, testosterone levels were measured and reviewed by an unblinded physician, who increased the daily testosterone dose to 15 g (3 active tubes) if the mean testosterone level was less than 17.35 nmol/L (500 ng/dL) or decreased it to 5 g (1 active tube plus 2 tubes of placebo gel) if the mean testosterone level was greater than 34.7 nmol/L (1000 ng/dL).	Blinding sufficiently described
Incomplete data (efficacy outcomes)	Low	Completion: Overall: 118/140 = 84% Testosterone: 16/70 = 86% Placebo: 58/70 = 83%	Completion rate > 80 percent and similar withdrawal rates between groups. Values for missing data were obtained by using multiple imputation for outcomes which were modeled.
Incomplete data (safety outcomes)	Low	"The frequency of adverse events did not differ between the 2 groups (Table 3)."	All patients randomized were included in the safety analysis. Adverse events were assessed at each visit
Behre 2012	Judgment	Quote	Comment
Sequence generation	Low	"Of the 1316 men screened, 362 were eligible for inclusion and they were randomized in parallel to receive testosterone gel (5 g, equivalent to 50 mg testosterone) or placebo gel (5 g) using a computer-based randomization system. Randomization was performed by the Central Randomization Group of Bayer Pharma AG (Berlin, Germany)."	Appears to be central randomization in a multicentre study; computer-based.
Allocation concealment	Low	"Randomization was performed by the Central Randomization Group of Bayer Pharma AG (Berlin, Germany)."	Appears to be central randomization in a multicentre study

Hackett 2013	Judgment	Quote	Comment
Blinding (objective outcomes)	Low	"Patients received testosterone gel or identical placebo gel in a foil sachet (2.5 or 5 g gel) for daily topical self-administration" "Double-blind treatment continued for 6 months" "To maintain blinding, total testosterone measurements were performed at the central laboratory. The investigator was warned if values of total testosterone were >28 nmol/L (>8.1ng/mL) and in these men the dosage was decreased until laboratory measurement values were indicating values <28 nmol/L"	Investigators may have become unblinded when "warned" by the laboratory of high testosterone values; however, this is not likely to impact objective outcomes
Blinding (subjective outcomes)	Low	"Patients received testosterone gel or identical placebo gel in a foil sachet (2.5 or 5 g gel) for daily topical self-administration" "Double-blind treatment continued for 6 months" "To maintain blinding, total testosterone measurements were performed at the central laboratory. The investigator was warned if values of total testosterone were >28 nmol/L (>8.1ng/mL) and in these men the dosage was decreased until laboratory measurement values were indicating values <28 nmol/L"	Blinding sufficiently described
Incomplete data (efficacy outcomes)	Low	"In total, 168/183 (91.8%) patients in the testosterone group and 155/179 (86.6%) in the placebo group completed the first 6 months of the study..."	Greater than 80% completion rate
Incomplete data (safety outcomes)	High	"The number of patients experiencing one or more serious adverse events was 7/183 (3.8%) and 6/179 (3.4%) in testosterone and placebo groups, respectively. Five patients experienced serious adverse events considered to be potentially related to the study medication (testosterone group). One patient was diagnosed with prostate cancer and subsequently treated with radical prostatectomy. Another underwent a prostate biopsy in which intraepithelial neoplasia was diagnosed and the third experienced a worsening of prostate-related symptoms which resolved following transurethral resection of the prostate (TURP). A fourth patient had a tendon rupture of the biceps and a fifth a deep vein thrombosis". "One patient in the testosterone group died of coronary artery disease; this cause of death was not considered related to the study medication."	SAEs were not reported in the placebo group were not reported to the same level of detail for as for the testosterone group
Zhang 2012	Judgment	Quote	Comment
Sequence generation	Unclear	"Eligible men were randomized to either an active treatment group or control group..."	Sequence generation not reported
Allocation concealment	Low	"Eligible men were randomized to either an active treatment group or control group in a single-blind fashion by sequentially numbered, opaque, sealed envelopes (SNOSE)"	Sequentially numbered, opaque, sealed envelopes were used
Blinding (objective outcomes)	Low	"single-blind fashion" "Men from both groups were similarly instructed about the study, but were unaware of which treatment group they would be assigned to and the drugs that were being used"	Personnel/outcome assessors were likely not blinded. Comparator group was a vitamin E/C capsule; unclear whether it was matched to the placebo treatment (oral). Not likely to impact objective outcomes
Blinding (subjective outcomes)	High	"single-blind fashion" "Men from both groups were similarly instructed about the study, but were unaware of which treatment group they would be assigned to and the drugs that were being used"	Personnel and outcome assessors were likely not blinded.
Incomplete data (efficacy outcomes)	Low	Overall completion: 160/160 = 100%. "No adverse effects were reported" "160 eligible men provided complete follow up". "One hundred and sixty eligible subjects were recruited and followed up data between December 1st 2009 and March 31st, 2012."	No withdrawals, and all randomized participants completed the study.
Incomplete data (safety outcomes)	Low	"No adverse effects were reported"	No withdrawals, and all randomized participants completed the study. 100%

Hackett 2013	Judgment	Quote	Comment
			completion rate.
Ho 2011	Judgment	Quote	Comment
Sequence generation	Unclear	"The present study was a double-blind, parallel, randomized, placebo-controlled trial with an allocation ratio of 1:1."	Sequence generation not reported
Allocation concealment	Low	"After reviewing the baseline assessment results, each participant received an intervention package indexed with a serial number at visit 1. Each package contained five vials of either all placebo or active medication, prepared in an identical form. Each serial number with its code for either placebo or active medication was kept in a sealed envelope. The supplier of the intervention packages and the envelopes was not involved in any stage of the trial."	Randomization code kept in a sealed envelope and managed by an independent supplier.
Blinding (objective outcomes)	Low	"After reviewing the baseline assessment results, each participant received an intervention package indexed with a serial number at visit 1. Each package contained five vials of either all placebo or active medication, prepared in an identical form. Each serial number with its code for either placebo or active medication was kept in a sealed envelope. The supplier of the intervention packages and the envelopes was not involved in any stage of the trial. Hence, the participants, clinical investigators and trial site manager were all blinded to the types of intervention until the trial period was over, when only then, the codes were revealed. Revealing the codes within the trial period was permitted only when there was an occurrence of serious adverse event."	Blinding well described
Blinding (subjective outcomes)	Low	"After reviewing the baseline assessment results, each participant received an intervention package indexed with a serial number at visit 1. Each package contained five vials of either all placebo or active medication, prepared in an identical form. Each serial number with its code for either placebo or active medication was kept in a sealed envelope. The supplier of the intervention packages and the envelopes was not involved in any stage of the trial. Hence, the participants, clinical investigators and trial site manager were all blinded to the types of intervention until the trial period was over, when only then, the codes were revealed. Revealing the codes within the trial period was permitted only when there was an occurrence of serious adverse event."	Blinding well described
Incomplete data (efficacy outcomes)	Low	"After excluding 164 men, 120 men were recruited and randomized equally into the treatment and placebo groups, but only 56 participants in the treatment and 58 in the placebo group completed the study. In the treatment group, one patient died from myocardial infarction while three withdrew from the study (one because of chest pain and another two because of relocation to another state). In the placebo group, one patient died from myocardial infarction and another withdrew because of chest pain."	Completion rate over 90% in both arms, and approximately equal in both arms
Incomplete data (safety outcomes)	Low	"After excluding 164 men, 120 men were recruited and randomized equally into the treatment and placebo groups, but only 56 participants in the treatment and 58 in the placebo group completed the study. In the treatment group, one patient died from myocardial infarction while three withdrew from the study (one because of chest pain and another two because of relocation to another state). In the placebo group, one patient died from myocardial infarction and another withdrew because of chest pain."	Completion rate over 90% in both arms, and approximately equal in both arms. All withdrawn participants are accounted for
Sheffield-Moore 2011	Judgment	Quote	Comment
Sequence generation	Unclear	"All men were randomized into the following groups ... by the UTMB Investigational Drug Service pharmacist."	Sequence generation not reported
Allocation	Low	"All men were randomized into the following groups ... by the	Allocation was done by a

Hackett 2013	Judgment	Quote	Comment
concealment		UTMB Investigational Drug Service pharmacist."	pharmacist; however, it is unclear how the sequence was concealed.
Blinding (objective outcomes)	Low	"We conducted a randomized, double-blinded trial ..."	No further detail provided; however, blinding is unlikely to influence objective outcomes
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Low	Completion: 24/24 (100%) "Leg strength measures were uncomfortable for one subject and were discontinued"	The authors reported that the data was only missing for one person who found it uncomfortable to undergo physical testing
Incomplete data (safety outcomes)	High	"Adverse events during the testosterone replacement phase of this study were reported to the UTMB Institutional Review Board and were not considered attributable to study participation. These adverse events were minimal and not limited to a specific treatment group."	Adverse events not adequately reported
Kaufman 2011	Judgment	Quote	Comment
Sequence generation	Unclear	"The randomization schedule was prepared by the Global Clinical Supplies Office of the study sponsor"	Sequence generation not reported in sufficient detail
Allocation concealment	Low	"Randomization was managed via an interactive voice response system"	Central allocation
Blinding (objective outcomes)	Low	"The investigator and subject were blinded to study gel medication assignment, and study medication identity was concealed by identical packaging."	Unclear whether outcome assessors were blinded; however, not likely to introduce bias because for objective outcomes
Blinding (subjective outcomes)	Low	"The investigator and subject were blinded to study gel medication assignment, and study medication identity was concealed by identical packaging."	Blinding appeared to be sufficient.
Incomplete data (efficacy outcomes)	High	Completion: Testosterone: 134/262 (72%); placebo: 28/40 (70%) "A similar percentage of subjects in the 1.62% testosterone gel group (66/234, 28.2%) and the placebo group (12/40, 30.0%) discontinued from the study."	Data for the efficacy (testosterone levels) are reported for the number of people who contributed a measurement on a given study day.
Incomplete data (safety outcomes)	Low	"All 274 subjects who were randomized were included in the safety sample." "No deaths occurred and a similar percentage of subjects in the testosterone and the placebo groups experienced a treatment-emergent serious AE. However, a higher proportion of subjects in the testosterone groups discontinued from the study, mostly due to PSA increases"	Discontinuations were well described with reasons. Rate of discontinuation was similar in both groups (28% in T-gel, 30% in placebo). Most withdrawals were due to adverse events in the TRT group; these were well described
Jones 2011	Judgment	Quote	Comment
Sequence generation	Unclear	"Subjects were randomized (1:1) to receive either ... Tostran ... or placebo gel once daily and stratified to treatment arms according to the presence of MetS only and type 2 diabetes with or without MetS."	Sequence generation not described
Allocation concealment	Unclear	"All individuals involved in monitoring, data management, or other study aspects were blinded to treatment."	Allocation concealment not described
Blinding (objective outcomes)	Low	"All individuals involved in monitoring, data management, or other study aspects were blinded to treatment." "Dummy dose changes were performed in the placebo group to maintain blinding."	Blinding appears to have been done

Hackett 2013	Judgment	Quote	Comment
Blinding (subjective outcomes)	Low	"All individuals involved in monitoring, data management, or other study aspects were blinded to treatment." "Dummy dose changes were performed in the placebo group to maintain blinding." "Subjects were randomized (1:1) to receive either ... Tostran ... or placebo gel"	Blinding appears to have been done. Through dummy dose changes, efforts were made to maintain blinding of participants
Incomplete data (efficacy outcomes)	High	Completion: overall 118/220 (54%); TRT: 60/112 (54%); placebo: 58/108 (54%) "The primary analysis of all end points was based on the intention-to-treat (ITT) population (all randomized patients)."" Unless otherwise stated, all efficacy data were analyzed in the ITT population." "...a last observation carried forward approach was used." "Of 518 patients screened, 220 were randomized (testosterone n = 108; placebo n = 112) and received at least one dose of study drug (ITT and safety populations)." "Two other populations were also studied: the perprotocol (PP) population (randomized patients who received \$1 dose of study medication with no protocol violations during the first 6 months of the study) and the modified PP (mPP) population. This latter population was established post hoc because the PP population was substantially reduced in size after exclusion of patients who took unauthorized concomitant medications from the ITT population (Supplementary Data)."	Completion rate was 54% in both groups. Reasons for exclusion were documented, although a lot of participants discontinued because they "withdrew consent". Although the primary planned analysis was ITT an inadequate method of handling missing data was used (LOCF)
Incomplete data (safety outcomes)	High	"Reasons for early withdrawal included protocol violation (n = 28), withdrawal of consent (n = 27), AEs (n = 26) and loss to follow-up (n = 9)."	Reasons for exclusion were provided by treatment group, although a lot of participants discontinued because they "withdrew consent" (TRT: 12; placebo: 15). Four patients in the TRT group and 6 patients in the placebo group were discontinued because of "other" reasons (not defined).
Shigehara 2011	Judgment	Quote	Comment
Sequence generation	Unclear	"After completion of all baselines tests, participants were randomly assigned to receive testosterone administration (ART group) and to the untreated control group"	Sequence generation not described
Allocation concealment	Unclear	"After completion of all baselines tests, participants were randomly assigned to receive testosterone administration (ART group) and to the untreated control group"	Not described
Blinding (objective outcomes)	Low	"After completion of all baselines tests, participants were randomly assigned to receive testosterone administration (ART group) and to the untreated control group"	Not blinded; control group was "no treatment"; unlikely to affect objective outcomes
Blinding (subjective outcomes)	High	"After completion of all baselines tests, participants were randomly assigned to receive testosterone administration (ART group) and to the untreated control group"	Not blinded; control group was "no treatment"; could introduce bias for subjective outcomes
Incomplete data (efficacy outcomes)	Low	Completion: 23/26 in each group = 88%.	All dropouts accounted for. Missing values not likely to have large effect on observed effect size
Incomplete data (safety outcomes)	Low	Completion: 23/26 in each group = 88%.	All dropouts accounted for. Reasons for withdrawal similar between groups.
Aversa 2010, p. 776	Judgment	Quote	Comment
Sequence generation	Unclear	"This was a randomized, double-blind, double-dummy study with three parallel treatment arms"	Sequence generation not described

Hackett 2013	Judgment	Quote	Comment
		"Each subject was randomized (1:1:3) to receive ... for 6 months"	
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"double-blind, double-dummy study"	Blinding not described beyond "double blind, double-dummy"; unlikely to affect ROB for objective outcomes
Blinding (subjective outcomes)	Low	"completion of IIEF-5, AMS, IPSS questionnaires by patient, blood sample for laboratory assessment were assessed at baseline and every 3 months" "double-blind, double-dummy study"	Blinding was described as double blind, double dummy.
Incomplete data (efficacy outcomes)	Unclear	Completion: Placebo: 9/10 (90%); oral TU: 10/10 (100%); IM TU: 31/32 (97%). "TU was safe over 12 months and discontinuation rates were similar to placebo"* *Cross-over study – after 6 mo, patients receiving oral TU were switched to IM TU	Number of patients assessed not provided for outcome measurements. Authors mention 'last observation carried forward' but do not provide further details; insufficient evidence to make a judgment
Incomplete data (safety outcomes)	Unclear	"...one patient was discontinued in the IM TU arm because of a rise in the hematocrit level above the normal range within 6 months, however the patient had a baseline level of 51% that was almost critical at the study entry. By contrast, in the P arm one patient was discontinued because of the occurrence of acute myocardial infarction"* "At last observation carried forward, there were two discontinuations due to prostate adverse events. One patients withdrew in the IM TU arm (mild and transient heritocytosis) and one in the P arm (acute myocardial infarction)" "TU was safe over 12 months and discontinuation rates were similar to placebo"	Although the completion rate was high, insufficient details were given to allow determination of when the events occurred (could not determine during which period the MI in placebo group occurred)
Kalinchenko 2010	Judgment	Quote	Comment
Sequence generation	Unclear	"A randomization procedure was followed with allocation probabilities of 0.7 and 0.3 for the active and placebo treatment groups."	Sequence generation was not described
Allocation concealment	Low	"The study medication was prepared by the manufacturing company of TU..." "Identification of trial medication was by numbered sealed packages, and each participant enrolled in the study was assigned one package. It only became apparent which packages had contained TU and which placebo until the code was broken for data analysis. Thus, investigators and patients were blinded until the end of the study."	Appears to have been central or pharmacy controlled allocation and used sealed packages.
Blinding (objective outcomes)	Low	"The study medication was prepared by the manufacturing company of TU (Nebido) (Bayer Schering Pharma, Berlin, Germany), and the packages were numbered. Only when the code was broken was it apparent which packages had contained TU and which placebo." "The placebo was an analogue of Nebido of the same appearance but without an active substance, containing the vehicle castor oil and benzyl benzoate."	Participants and investigators were blinded. Unclear if outcome assessors were blinded; however, this is unlikely to introduce bias for objective outcomes
Blinding (subjective outcomes)	Low	"The study medication was prepared by the manufacturing company of TU (Nebido) (Bayer Schering Pharma, Berlin, Germany), and the packages were numbered. Only when the code was broken was it apparent which packages had contained TU and which placebo." "The placebo was an analogue of Nebido of the same appearance but without an active substance, containing the vehicle castor oil and benzyl benzoate."	Method of blinding is reported and judged to be sufficient to ensure blinding of subjects for self-assessment of subjective outcomes
Incomplete data (efficacy outcomes)	Low	Completion: TRT: 105/113 (92.9%); placebo: 65/71 (91.5%) "Of the total of 184 men, 14 dropped out of the study (six receiving placebo and eight receiving TU). This resulted in 105 (92.9%) men receiving TU and 65 (91.5%) receiving placebo completing the trial."	Efficacy based on completers (no imputation), but similar high level of completion in each group. (> 80%)

Hackett 2013	Judgment	Quote	Comment
Incomplete data (safety outcomes)	Low	Completion: TRT: 105/113 (92.9%); placebo: 65/71 (91.5%) "Of the total of 184 men, 14 dropped out of the study (six receiving placebo and eight receiving TU). This resulted in 105 (92.9%) men receiving TU and 65 (91.5%) receiving placebo completing the trial."	TRT: 8 discontinued (of 113); Placebo: 6 discontinued (of 71). The number and reason for each discontinuation is described. Only one patient in the TRT group was "lost to follow-up"
Aversa 2010, p. 3495	Judgment	Quote	Comment
Sequence generation	Unclear	NR	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation not described
Blinding (objective outcomes)	Low	"The study was randomized, double-blind, double-dummy with two parallel treatment arms..." "To ensure that treatment remained blinded, a standard double-dummy technique was used. All patients received ampoule for injections, either TU or a visually identical placebo injection and gel packets containing placebo preparations."	Sufficiently blinded for objective outcomes
Blinding (subjective outcomes)	Low	"The study was randomized, double-blind, double-dummy with two parallel treatment arms..." "To ensure that treatment remained blinded, a standard double-dummy technique was used. All patients received ampoule for injections, either TU or a visually identical placebo injection and gel packets containing placebo preparations."	Blinding appears to have been sufficient
Incomplete data (efficacy outcomes)	Low	"...and a mixed linear regression model on repeated measures data (for between-group comparisons across all time points) to analyze data for an Intent to Treat Group (including all subjects enrolled and treated in this trial with values imputed for their Last Observation Carried Forward [LOCF] for any subjects who did not complete the trial) and a Completer's Group including only data from subjects who completed the trial per protocol)" "After 12 months, a primary analysis, including a total of 50 patients randomized, was performed."	LOCF mentioned but is not necessarily an appropriate way to impute missing data. The authors do not report outcomes based on the per protocol population, although they state that there was a "completers group" analysis including only the per protocol analysis. However, completion was > 80% at 12 mo
Incomplete data (safety outcomes)	Low	"At LOCF, four patients were discontinued from the study. One patient in the PLB group experienced an acute myocardial infarction and three patients in the TU group experienced mild erythrocytosis."	It seems that only 4 patients discontinued the trial before 12 months and all are accounted for. It is unclear whether there were any withdrawals after 12 mo; however, all patients received TU during that period (not included in data analysis)
Kenny 2010	Judgment	Quote	Comment
Sequence generation	Unclear	"The randomization was done using blocked randomization with random block sizes (2 or 4), stratified according to frailty status."	Sequence generation not well described
Allocation concealment	Low	"The research pharmacist, who had no direct contact with research participants, labeled and distributed gel."	Pharmacist labeled and distributed study medication
Blinding (objective outcomes)	Low	"Men randomized in a double-masked manner to receive transdermal testosterone supplementation (5 mg AndroGel 1% Solvay Pharmaceuticals, Brussels, Belgium) or a matching,	Blinding sufficient for objective outcomes

Hackett 2013	Judgment	Quote	Comment
		indistinguishable placebo gel[...]Investigators and subjects were unaware of the content of the gel bottles."	
Blinding (subjective outcomes)	Low	"Men randomized in a double-masked manner to receive transdermal testosterone supplementation (5 mg AndroGel 1% Solvay Pharmaceuticals, Brussels, Belgium) or a matching, indistinguishable placebo gel... Investigators and subjects were unaware of the content of the gel bottles."	Blinding sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion: Overall (end of therapy; mean 23 mo): 62/131 (47.3%); TRT: 36/69 (52.2%); Placebo: 26/62 (41.9%) "The study was designed as a 2-year intervention, but because of delays in recruitment and lack of funds for an extension, limited 24-month follow-up is available. An "end therapy" time point was created for analysis and was defined as men who completed at least 16 months of follow-up (mean 23 months, n=62). Follow-up is available for all men who did not discontinue because of illness or complication (n=99, 75%) at 12 months."	75% completed 12 months of follow-up. An "end of therapy time point includes only 62 of 133 (47.3%) randomized participants. No data is available regarding the 24-month planned follow-up.
Incomplete data (safety outcomes)	Unclear	Completion: 12 mo: placebo 46/62 (74.2%); TRT: 53/69 (76.8%). End of study: overall: 62/131 (47.3%); TRT: 36/69 (52.2%); Placebo: 26/62 (41.9%)	Reasons for withdrawals before 12 months or end of treatment are well described; drop-out rates are high and variable between groups.
Basaria 2010	Judgment	Quote	Comment
Sequence generation	Low	"...computer-generated randomization tables, using a block size of 6"	Computer-generated randomization tables sufficient for low ROB
Allocation concealment	Low	"Eligible subjects were stratified by age (65-75 and >75) and randomized to placebo or testosterone gel based on concealed, computer-generated randomization tables, using a block size of 6. Study personnel and participants were blinded to randomization assignment"	Randomization tables were "concealed" and study personnel and participants were blinded
Blinding (objective outcomes)	Low	"...participants and outcome assessors were blinded to intervention" "Study personnel and participants were blinded to randomization assignment" "All subjects received three gel tubes daily in various concentrations of placebo and testosterone to maintain blinding"	Blinding sufficient for objective outcomes
Blinding (subjective outcomes)	Low	"...participants and outcome assessors were blinded to intervention" "Study personnel and participants were blinded to randomization assignment" "All subjects received three gel tubes daily in various concentrations of placebo and testosterone to maintain blinding"	Blinding sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	Low	Completion: overall 176/209 (84%). At 12 weeks: TRT 92/106 (86.8); placebo: 91/103 (88.3)	Completion over 80%
Incomplete data (safety outcomes)	Unclear	*At the time when further enrollment was stopped and study medication was discontinued due to DSMB's recommendations, 209 men had been randomized ...and 107 (54 in testosterone and 53 in placebo group) had completed all phases of the study. An additional 22 men (11 in each group) had completed the full 24-weeks of study medication. Amongst those who did not complete the study either because they were lost to follow-up or discontinued because of DSMB's directive or for other reasons, 47 men (including 24 men (13 in testosterone and 11 in the placebo arm) who were lost to follow-up or discontinued due to adverse events plus 23 men (15 in testosterone and 8 in placebo arm) who were discontinued per DSMB's directive had received at least 12-weeks of study medication and had undergone at least one post-randomization outcome assessment. These 176 men, who had completed baseline assessments and at least one post-randomization efficacy assessment, were eligible for analyses of	This trial was stopped early by the DSMB; withdrawals are accounted for; however, we can't determine how many were due to loss-to-follow-up (grouped with adverse events)

Hackett 2013	Judgment	Quote	Comment
		efficacy data. All 209 randomized men were included in the adverse event analyses. Of the 50 randomized subjects, who dropped out, were lost-to-follow up or discontinued, 27 (13 in the testosterone arm and 14 in the placebo arm) dropped out or were discontinued due to adverse events listed below. The adverse events reported by these 27 men included reaction to study gel (n=8), sleep disturbances (n=3), cardiovascular-related event (n=4), prostate-related (n=3), medical co-morbidities (n=3), high hematocrit (n=1), musculoskeletal (n=1), gastrointestinal bleeding (n=1), neuropathy (n=1), asthma exacerbation (n=1), and lung cancer (n=1).	
Srinivas-Shankar 2010	Judgment	Quote	Comment
Sequence generation	Low	"Participants were randomized into active and placebo groups in blocks of 10 by computer-generated sequence produced by the trial pharmacist, who had no contact with research participants." "A randomized double-blind, placebo-controlled study"	Computer-generated randomization
Allocation concealment	Low	"Participants were randomized into active and placebo groups in blocks of 10 by computer-generated sequence produced by the trial pharmacist, who had no contact with research participants."	Pharmacy-controlled allocation
Blinding (objective outcomes)	Low	"Precautions were taken to ensure that the outcome assessor, monitoring clinician, and the nurses remained unaware of trial medication type/dose for individual participants. For any given participant, the presence or absence of a dose adjustment did not provide sufficient information to determine which treatment had been allocated, except possibly in 27 participants who required dose reduction." "double blind placebo controlled" "those in the control group received matched placebo gel"	Blinding was sufficient for objective outcomes
Blinding (subjective outcomes)	Low	"Precautions were taken to ensure that the outcome assessor, monitoring clinician, and the nurses remained unaware of trial medication type/dose for individual participants. For any given participant, the presence or absence of a dose adjustment did not provide sufficient information to determine which treatment had been allocated, except possibly in 27 participants who required dose reduction." "double blind placebo controlled" "those in the control group received matched placebo gel"	Blinding was sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	Low	"The primary analysis included all randomized participants completing baseline assessment on an intention-to-treat basis." "274 met the recruitment criteria and were randomized into T (138) and placebo groups (136). "Twelve men withdrew before baseline assessment" (T 8 and P 4) "and 31 men after commencing treatment." (T 16 and P 15) Completion: 84% (based on 43/274 withdrawals); treatment compliance was assessed by self-report,	Method of imputation for missing data not reported; however, completion rate is above 80% and roughly equal for both groups
Incomplete data (safety outcomes)	Unclear	"274 met the recruitment criteria and were randomized into T (138) and placebo groups (136). "Twelve men withdrew before baseline assessment" (T 8 and P 4) "and 31 men after commencing treatment." (T 16 and P 15). Withdrawals are documented with reasons in CONSORT style document Some withdrew because they were "not interested" (P 4; T 2) or "did not want to continue" (P 1 T 0). Three men in the testosterone group could not be contacted.	All missing people appear to be accounted for; however, 5 people in each group discontinued because they weren't interested or were lost to follow-up – unknown if they weren't interested in continuing because of an adverse effect
Hohl 2009	Judgment	Quote	Comment
Sequence generation	High	The first randomized patient received Deposteron, the second patient received Durateston, and the third patient received Nebido and so on."	Study randomized via alternation

Hackett 2013	Judgment	Quote	Comment
Allocation concealment	High	The first randomized patient received Deposteron, the second patient received Durateston, and the third patient received Nebido and so on."	Allocation could be predicted by investigators
Blinding (objective outcomes)	Low	NR	Blinding not reported, but unlikely to introduce bias for objective outcomes
Blinding (subjective outcomes)	Unclear	NR	Blinding not reported; may introduce bias for subjective outcomes
Incomplete data (efficacy outcomes)	Low	No mention of completion or withdrawals, but "after" tables show 32 men (equal to the number randomized)	Apparent 100% completion in all groups
Incomplete data (safety outcomes)	Low	No mention of completion or withdrawals; however, "after" tables show 32 men (equal to the number randomized); however, there was no reporting of adverse events	Apparent 100% completion, all groups; no reporting of withdrawals, SEs, etc
Morales 2009	Judgment	Quote	Comment
Sequence generation	Low	"Participants were allocated at random to one of the three cohorts." "randomly permuted blocks of size nine"	Permuted block randomization indicates computer generation
Allocation concealment	Low	"Blinded treatment packages were prepared and assigned by a central pharmacist."	Allocation was controlled by a central pharmacy
Blinding (objective outcomes)	Low	"Men fulfilling the criteria were offered participation in a placebo-controlled, randomized, double blind, double dummy, fixed dose study..."	Blinding sufficient for objective outcomes
Blinding (subjective outcomes)	Low	"Men fulfilling the criteria were offered participation in a placebo-controlled, randomized, double blind, double dummy, fixed dose study..." Blinded treatment packages were prepared and assigned by a central pharmacist using randomly permuted blocks of size nine.	Double blind, central preparation of blinded treatment packages.
Incomplete data (efficacy outcomes)	Low	Completion: TRT: 24/29 (83%); placebo 28/29 (97%). Withdrawals in the TRT group were due to AEs (2), lack of efficacy (1), loss to follow-up (1). One patient in the TRT group was not assessed at baseline. One loss in the placebo group was due to loss to follow-up.	Overall completion rate was greater than 80%; there was a differential drop out rate between groups but numbers are small, and all losses were accounted for.
Incomplete data (safety outcomes)	Low	Completion: TRT: 24/29 (83%); placebo 28/29 (97%). Withdrawals in the TRT group were due to AEs (2), lack of efficacy (1), loss to follow-up (1). One patient in the TRT group was not assessed at baseline. One loss in the placebo group was due to loss to follow-up.	All participants who received at least one dose were included in safety analysis
Heufelder 2009	Judgment	Quote	Comment
Sequence generation	Low	"The procedure of randomization followed recommendations as described in Kenjo et al (2000)"	Kenjo et al 2000 describes a computer-based randomization method.
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"The study design was single blind; that is, study personnel were not aware of the treatment arm to which participants were randomized, and participants were instructed by the prescribing physician not to disclose their treatment to study personnel.	Single blind, but patient knowledge of treatment group is unlikely to affect objective outcomes
Blinding (subjective outcomes)	High	"The study design was single blind; that is, study personnel were not aware of the treatment arm to which participants were randomized, and participants were instructed by the prescribing physician not to disclose their treatment to study personnel.	Single blind; participants were aware of assignment

Hackett 2013	Judgment	Quote	Comment
Incomplete data (efficacy outcomes)	Low	"All participants completed the study without adverse effects and without protocol violations" Probably, as a result of frequent interactions between staff and participants, compliance with diet and exercise was 100%, and none of the participants dropped out of the study	All patients completed the study
Incomplete data (safety outcomes)	Low	"All participants completed the study without adverse effects and without protocol violations" Probably, as a result of frequent interactions between staff and participants, compliance with diet and exercise was 100%, and none of the participants dropped out of the study	All patients completed the study
Caminiti 2009	Judgment	Quote	Comment
Sequence generation	Unclear	"Patients were randomly allocated to receive, on top of optimal medical therapy, either intramuscular (IM) long-acting testosterone undecanoate (1,000 mg Nebido, BayerSchering, Berlin, Germany) or IM saline injection at baseline and at 6 and 12 weeks" "Testosterone and placebo were dispensed by the Pharmacologic Department, which was also responsible for the randomization codes."	Sequence generation not reported.
Allocation concealment	Low	"Patients were randomly allocated to receive, on top of optimal medical therapy, either intramuscular (IM) long-acting testosterone undecanoate (1,000 mg Nebido, BayerSchering, Berlin, Germany) or IM saline injection at baseline and at 6 and 12 weeks" "Testosterone and placebo were dispensed by the Pharmacologic Department, which was also responsible for the randomization codes."	Allocation concealment not well described, but appears to be pharmacy-controlled allocation
Blinding (objective outcomes)	Low	"Testosterone and placebo were dispensed by the Pharmacologic Department, which was also responsible for the randomization codes. The drug was administered by a nurse, and the investigators were kept blinded on patient treatment" "Patients were randomly allocated to receive, either intramuscular (IM) longacting testosterone undecanoate (1,000 mg Nebido, Bayer-Schering, Berlin, Germany) or IM saline injection at baseline and at 6 and 12 weeks."	Patients and investigators were blinded.
Blinding (subjective outcomes)	Low	"Testosterone and placebo were dispensed by the Pharmacologic Department, which was also responsible for the randomization codes. The drug was administered by a nurse, and the investigators were kept blinded on patient treatment" "Patients were randomly allocated to receive either intramuscular (IM) long-acting testosterone undecanoate (1,000 mg Nebido, Bayer-Schering, Berlin, Germany) or IM saline injection at baseline and at 6 and 12 weeks."	Blinding sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	Low	Completion: TRT: 31/35 (88.5%); placebo: 33/35 (94.3%) "Of 70 patients, 64 completed the study protocol: 4 patients in the testosterone group and 2 in the placebo group discontinued the study."	All withdrawals accounted for, with general reasons provided. However, analysis appears to be based on participants who provided data after treatment
Incomplete data (safety outcomes)	Low	"The reason for discontinuation, in every case, was the willingness of the patient to escape from the study (e.g., logistic reasons, moving to another region, autonomous decision to discontinue the protocol not related to testosterone supplementation)"	Reasons for withdrawals provided and do not seem related to treatment
Mathur 2009	Judgment	Quote	Comment
Sequence generation	Low	"Randomisation was determined by computer-generated random numbers"	Computer-generated random numbers
Allocation concealment	Unclear	"This was a double-blind, randomised, parallel group placebo-controlled trial."	Allocation concealment not described

Hackett 2013	Judgment	Quote	Comment
Blinding (objective outcomes)	Low	"The trial drug used in this study is a novel long-acting depot preparation of testosterone requiring only four injections per year with an additional loading dose after the first 6 weeks, or matching placebo."	Blinding not well described, although placebo is 'matched' and double-blind
Blinding (subjective outcomes)	Low	"The trial drug used in this study is a novel long-acting depot preparation of testosterone requiring only four injections per year with an additional loading dose after the first 6 weeks, or matching placebo."	Described as double-blind, with a matched placebo
Incomplete data (efficacy outcomes)	Low	"Treatment effect as measured by EuroQol ..., Beck Depression Inventory... and Seattle Angina Score ... appeared unchanged" "Two patients withdrew early in the trial before any outcome assessment could be made, therefore complete data was available on 13 patients"	No subjective outcomes reported. Although the authors say that they looked at QoL and depression, they do not report data beyond saying that there was no change. Judged as high for the outcomes that we were able to extract data for (T levels) because of high completion rate
Incomplete data (safety outcomes)	High	"Two patients withdrew early in the trial before any outcome assessment could be made, therefore complete data was available on 13 patients" "Nebido injections were well tolerated and no patient suffered any major adverse event or unplanned hospital admission."	One patient withdrew from each group. Reason for withdrawal not reported for patient who withdrew from the control group
Shores 2009	Judgment	Quote	Comment
Sequence generation	Low	"Randomization was done via a computer random-number-generator program for a 1:1 ratio assignment."	Computer-generated random numbers
Allocation concealment	Low	"Subjects were randomly assigned to receive either placebo gel or testosterone gel by a research pharmacist who was blinded to the subjects' ratings and assessments. Randomization was done via a computer random-number-generator program for a 1:1 ratio assignment."	Pharmacy-controlled allocation
Blinding (objective outcomes)	Low	"All raters were blinded to the subjects' treatment status during the double-blind phase." "A placebo of the same formulation as the testosterone treatment was used for blinding."	Blinding adequate for objective outcomes
Blinding (subjective outcomes)	Low	"All raters were blinded to the subjects' treatment status during the double-blind phase." "A placebo of the same formulation as the testosterone treatment was used for blinding."	Blinding adequate for subjective outcomes
Incomplete data (efficacy outcomes)	High	Overall: 27/33 (81.8%); TRT: 12/17 (70.6%); placebo: 15/16 (93.8%) "In all analyses of primary and secondary outcomes, we used an intent-to-treat approach, and the last-observation-carried-forward (LOCF) method was applied for missing data".	Although the overall completion rate is above 80%, the rate is variable between groups. LOCF may not be appropriate for imputation of missing data and may introduce bias
Incomplete data (safety outcomes)	High	Overall: 27/33 (81.8%); TRT: 12/17 (70.6%); placebo: 15/16 (93.8%)	Men who discontinued treatment were significantly younger and had significantly higher baseline free testosterone levels. Dropout reasons were provided but the rate was considerably higher in the TRT group; 1 loss to follow-up and 1 left because he didn't like the gel
Chiang 2009	Judgment	Quote	Comment

Hackett 2013	Judgment	Quote	Comment
Sequence generation	Unclear	"This was a double-blind, randomized, placebo-controlled, 3-month study" "No statistically significant differences were found in the baseline data of the testosterone level between the TTG group and the placebo group"	Sequence generation was not described
Allocation concealment	Unclear	NR	Allocation concealment was not described
Blinding (objective outcomes)	Low	"double-blind, randomized, placebo-controlled" "No distinguishable feature could be noted between the TTG and the placebo. All the patients were instructed to apply the gel once daily to 2 alternating application sites, such as the shoulder, upper arm, and/or abdomen."	Participants were blinded and the method of blinding was described. Blinding of outcome assessors was not addressed; however, this is unlikely to affect objective outcomes
Blinding (subjective outcomes)	Low	"double-blind, randomized, placebo-controlled" "No distinguishable feature could be noted between the TTG and the placebo. All the patients were instructed to apply the gel once daily to 2 alternating application sites, such as the shoulder, upper arm, and/or abdomen."	Patients were blinded and the method of blinding was described. "double-blind"
Incomplete data (efficacy outcomes)	High	Completion: overall 30/40 (75%); TRT: 15/20 (75%); placebo: 15/20 (75%) "Seven patients did not complete the follow-up of either the biochemical tests or questionnaires and were thus excluded from the analysis. Thus, 30 patients (15 in the treatment group and 15 in the control group) who completed the whole evaluation, including the IIEF-15 and IIEF-5 questionnaires in the 3-month study." "The sample size was small, and $\leq 25\%$ of the patients were withdrawn or excluded from the analysis because of side effects or incomplete data"	Reasons not provided for the seven patients who did not complete analysis. More than $> 20\%$ were withdrawn and excluded from the analysis.
Incomplete data (safety outcomes)	High	"Three patients in the placebo group were withdrawn from the study because of adverse events. Two of them were drug-related adverse events (skin rash and dermatitis). The other was a nondrug-related event (abdominal pain). Seven patients did not complete the follow-up of either the biochemical tests or questionnaires and were thus excluded from the analysis." "The sample size was small, and $\leq 25\%$ of the patients were withdrawn or excluded from the analysis because of side effects or incomplete data"	Reasons not provided for the seven patients who did not complete analysis.
Emmelot-Vonk 2009	Judgment	Quote	Comment
Sequence generation	Low	"A randomization list was computer generated by Organon NV, Oss, The Netherlands. One box with active medication and one box with placebo medication were delivered at the UMC Utrecht Pharmacy with the randomization list." "A randomization list without stratification using blocks of 6 was computer-generated by Organon NV...." "Randomization numbers were assigned to the subjects in orders of enrolment into the trial."	Computer-generated randomization list
Allocation concealment	Low	"A randomization list was computer-generated by Organon NV, Oss, The Netherlands. One box with active medication and one box with placebo medication were delivered at the UMC Utrecht Pharmacy with the randomization list. Pharmacy personnel labeled the jars for the participants and provided the study medication upon prescription of the trial physician. Randomization numbers were assigned to the subjects in orders of enrolment into the trial. The key to randomization numbers (ie, study drug allocation) was available 24 hours per day at the pharmacy department at the University Medical Center Utrecht only."	Pharmacy-controlled allocation
Blinding (objective outcomes)	Low	"This study had a randomized, double-blind, placebo-controlled design" "To assess the efficacy of blinding, the participants were asked at the end of intervention whether they thought they had	Judged low risk given that study was double blind, blinding method was

Hackett 2013	Judgment	Quote	Comment
		been assigned to the placebo or testosterone group." "Unblinding did not occur during the trial"	described, and unblinding did not occur during the trial.
Blinding (subjective outcomes)	Low	"This study had a randomized, double-blind, placebo-controlled design" "To assess the efficacy of blinding, the participants were asked at the end of intervention whether they thought they had been assigned to the placebo or testosterone group." "Unblinding did not occur during the trial"	Judged low risk given that study was double blind, blinding method was described, and unblinding did not occur during the trial.
Incomplete data (efficacy outcomes)	Low	Completion: overall 223/237 = 94%; testosterone: 104/120 = 87%; placebo: 103/120 = 88% "Because the percentage of missing data was very small (<3.6%), we did not use any specific strategies to handle this and the missing data were treated as missing values in the analysis. In an alternate analysis, we imputed missing values using a regression-based imputation method." "All analyses will be based on an intention-to-treat approach (i.e., the intention- to-treat group will consist of all subjects, including those who withdrew from blinded medication, who received at least one dose of study drug and who had at least one post-baseline assessment of the outcome variable)"	Judged low risk, given that the completion rate was > 80 %, the percent of missing data was small and imputation measures were implemented.
Incomplete data (safety outcomes)	Low	"All analyses will be based on an intention-to-treat approach (i.e., the intention- to-treat group will consist of all subjects, including those who withdrew from blinded medication, who received at least one dose of study drug and who had at least one post-baseline assessment of the outcome variable)"	The authors report attrition with reasons in each group along with exclusion in detail. They considered everyone who had at least one dose of study drug, and who had at least one post-baseline assessment in their analyses.
Agledahl 2008	Judgment	Quote	Comment
Sequence generation	Unclear	"Subjects were randomly assigned to receive either testosterone treatment ... or identically looking placebo"	Sequence generation not described
Allocation concealment	Unclear	"Subjects were randomly assigned to receive either testosterone treatment ... or identically looking placebo"	Allocation concealment not described
Blinding (objective outcomes)	Low	"Twenty-six men with subnormal testosterone levels ((11.0 nmol/L) were randomly assigned to treatment with intramuscular testosterone or placebo for one year in a double-blinded study" "...identically looking placebo (n=13) (placebo for testosterone undecanoate; Bayer Schering Pharma, Germany)."	Matched placebo was used and study is described as double blind
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Low	Completion: placebo = 100%; Nebido = 13/14 = 93%	One patient not included in analysis because he did not consume the test meal at the second oral fat load
Incomplete data (safety outcomes)	Low	"Of the 27 men enrolled in the study, one discontinued because he was unable to consume the test meal at the second oral fat load."	No safety outcomes reported, but it appears that all except one patient completed the trial.
Basurto 2008	Judgment	Quote	Comment
Sequence generation	Low	"A randomization without stratification was computer-generated and randomization numbers were assigned to the subjects in orders of enrolment into the trial"	Computer-generated randomization
Allocation concealment	Low	"Only the pharmacist knew of the randomization, neither the participants nor the radiologist and laboratory technicians knew the content of the injections until the entire study was completed"	Pharmacy-controlled allocation

Hackett 2013	Judgment	Quote	Comment
		"Pharmacy personnel labelled the injections for the participants and provided the medication upon prescription of the physician."	
Blinding (objective outcomes)	Low	"Only the pharmacist knew of the randomization, neither the participants nor the radiologist and laboratory technicians knew the content of the injections until the entire study was completed" "The placebo injections were identical in appearance to the testosterone injections" "Randomized, double-blind, placebo-controlled study"	Blinding well described
Blinding (subjective outcomes)	Low	"Only the pharmacist knew of the randomization, neither the participants nor the radiologist and laboratory technicians knew the content of the injections until the entire study was completed" "The placebo injections were identical in appearance to the testosterone injections" "Randomized, double-blind, placebo-controlled study"	Blinding well described
Incomplete data (efficacy outcomes)	Low	Completion: Overall: 42/48 =87.5%; placebo: 21/23 (91%); TRT: 21/25 (84%) "Intention-to-treat analysis was performed; for 6 subjects who did not complete the protocol the baseline observation of BMD was carried forward to final time points."	Completion rates overall, and in both groups, were all >80%
Incomplete data (safety outcomes)	Unclear	"Six subjects did not complete the study for the following reasons: increment of PSA (three were in the treated group) and lost to follow-up (two were in the control group, and one was in the treated group)" "During the study three out of 25 treated patients had a moderate elevation in PSA levels between 4.3 and 5.0 ng/mL). These participants were excluded from the study; after discontinuation of the testosterone treatment, PSA level normalized, and they were thoroughly evaluated by the consultant urologist who ruled out malignancy in the prostate. Haematocrit values showed a significant (p<0.05) increment in the group compared with the placebo group (from 44.7±5.2% to 46.4±4.3%) but within the normal range [12]. No subject experienced an increase above the upper limit of normal (52%); neither required suspension of therapy [12–13]. Serum liver enzymes remained unchanged during the study."	Reason for withdrawal provided for each participant. Loss to follow-up is comparable between groups. Rated as unclear because of the possibility that the lost participants experienced an AE.

Svartberg 2008	Judgment	Quote	Comment
Sequence generation	Unclear	"Those consenting were randomly allocated in a double-blind fashion to receive either testosterone treatment ... or identically looking placebo... ."	Sequence generation not described
Allocation concealment	Unclear	"Those consenting were randomly allocated in a double-blind fashion to receive either testosterone treatment ... or identically looking placebo... ."	Allocation concealment not described
Blinding (objective outcomes)	Low	"Those consenting were randomly allocated in a double-blind fashion to receive either testosterone treatment with an intramuscular depot injection of testosterone (testosterone undecanoate 1000 mg, Nebido, Bayer Schering Pharma AG, BerlinGermany) or identically looking placebo (placebo for testosterone undecanoate, Bayer Schering Pharma AG, Germany)."	Double-blind, matched placebo
Blinding (subjective outcomes)	Low	"Those consenting were randomly allocated in a double-blind fashion to receive either testosterone treatment with an intramuscular depot injection of testosterone (testosterone undecanoate 1000 mg, Nebido, Bayer Schering Pharma AG, BerlinGermany) or identically looking placebo (placebo for testosterone undecanoate, Bayer Schering Pharma AG, Germany)."	Description of blinding sufficient
Incomplete data	Low	Completion: placebo: 18/19 (95%); TRT 17/19 (89.5%)	High completion, with only

Hackett 2013	Judgment	Quote	Comment
(efficacy outcomes)			one participant difference between groups
Incomplete data (safety outcomes)	Unclear	"One participant from each group withdrew from the study without stating reason, and one participant in the treatment group died from cardiac arrhythmia, which was not considered related to the testosterone therapy."	Unknown why two participants did not complete the study
Raynaud 2008	Judgment	Quote	Comment
Sequence generation	Unclear	"Randomized, open label, multicenter 1-year study"	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"Randomized, open label, multicenter 1-year study" "Testopatch® is a Pierre Fabre Medicament Laboratories' testosterone-in-adhesive-based matrix patch." "The patient in the second group received an IM injection of testosterone enanthate 250 mg (Androtardyl®), every 3 weeks."	Open label; however, not likely an issue for objective outcomes, but could affect withdrawals due to adverse events
Blinding (subjective outcomes)	High	"Randomized, open label, multicenter 1-year study" "Testopatch® is a Pierre Fabre Medicament Laboratories' testosterone-in-adhesive-based matrix patch." "The patient in the second group received an IM injection of testosterone enanthate 250 mg (Androtardyl®), every 3 weeks."	Subjective outcomes may have been affected by participants' knowledge of their assignment
Incomplete data (efficacy outcomes)	High	"65 patients (29.0%) withdrew from the study: 57 (30.3%) from the patch group (38 during the first 3 months), and 8 (22.2%) from the IM group. Reasons for withdrawal in the patch group were application site disorders (20), adhesiveness (13) and insufficient response (8)." "The intent-to-treat (ITT) efficacy data set was based on all randomized patients with a baseline value and at least one available assessment under treatment." "Missing data were not estimated for hormone parameters. Missing items in clinical scores were replaced by the mean of the non-missing items."	Unequal withdrawal rates in the groups, and some patients withdrew because of insufficient response. Withdrawal rate >20%.
Incomplete data (safety outcomes)	High	In the patch group, one patient died after the first 6 months of treatment following a spinal cord compression. 133 patients (71.5%) experienced at least 1 treatment-emergent AE (TEAE), 27 patients (14.5%) discontinued the study due to at least one AE and 9 patients (4.8%) experienced at least one serious adverse event (SAE). The most common events were infections (23.7%), administration site reactions (23.1%), gastrointestinal disorders (12.9%) and lipid disorders (9.7%). In the IM group, 27 patients (81.8%) experienced at least 1 TEAE and 3 patients (9.1%) experienced 1 SAE. No patient discontinued the study because of a TEAE. The most common events were infections (36.4%), muscle disorders (24.3%), gastrointestinal disorders (18.2%), lipid disorders (12.1%) and headache (12.1%).	Incomplete reporting of AEs. Only the most common events are reported.
Chiang 2007	Judgment	Quote	Comment
Sequence generation	Unclear	"A randomized, double-blind, placebo-controlled trial was conducted..."	Sequence generation was not described
Allocation concealment	Unclear	"A randomized, double-blind, placebo-controlled trial was conducted..."	Allocation concealment was not described
Blinding (objective outcomes)	Low	"A randomized, double-blind, placebo-controlled trial was conducted..." "Group A received testosterone gel" "Group B received a placebo gel. "	Method of blinding sufficiently described for objective outcomes
Blinding (subjective outcomes)	Unclear	"A randomized, double-blind, placebo-controlled trial was conducted..." "Group A received testosterone gel" "Group B received a placebo gel. "	Method of blinding not sufficiently described for subjective outcomes
Incomplete data (efficacy)	High	"There were 38 subjects in the ITT population for efficacy and safety evaluations, and 36 patients (20 in group A, 16 in group B)	Completion rate below 80% in placebo group, and no

Hackett 2013	Judgment	Quote	Comment
outcomes)		completed the 3-month study." "The intent-to-treat (ITT) population, defined as all randomized subjects who had taken at least one dose of medication and had at least one follow-up visit, was the basis for efficacy and safety evaluations" "The reasons of exclusion included relatively high screening TT level (14), elevated PSA level (8), low urinary flow rate (4) and other nonmedical reasons including their wives' disagreements (12)." ITT population = P 18 T 20 Total T (Table 1) = P baseline 18, 1 and 2 mo 17, T 20 IEF (Table 4) = 3 mo P 15, T 20 IPSS (Table 4) = 3 mo P17, T 20 Total withdrawals = P 4/20, T 0/20 Completion rate based on total withdrawals: P 80%, T 100%, overall 90%	mention of how missing data were addressed
Incomplete data (safety outcomes)	Low	Included in safety analysis: Placebo: 18/20 (90%); TRT: 20/20 (100%) "Of the 38 subjects, 16 (42%) reported one or more AEs, 8 subjects (40%) in the TTG group (n ¼ 20) and 8 (44%) in the placebo group (n = 18). A total of 32 AEs were reported, 13 in the TTG group and 19 in the placebo group (Table 5).	Adverse events are reported by group in Table 5; all participants in safety analysis appear to be accounted for
Marks 2006	Judgment	Quote	Comment
Sequence generation	Unclear	"The randomization table was generated and maintained by a biostatistician, who had no direct patient involvement"	Method of sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months" "All injections and clinical data collection were performed by a research coordinator (M.L.M.), who was kept blinded to group assignment" "Laboratory tests and data analysis were performed by personnel who were blinded to group assignment"	A matching placebo was used and sufficient details were provided regarding blinding
Blinding (subjective outcomes)	Low	"Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months" "All injections and clinical data collection were performed by a research coordinator (M.L.M.), who was kept blinded to group assignment" "Laboratory tests and data analysis were performed by personnel who were blinded to group assignment"	Blinding sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	Low	Completion: Overall: 40/44 (90.9%); TRT: 21/22 (95.5%); placebo: 19/22 (86%) "One participant assigned to receive TRT was terminated from the study early because of treatment-related erythrocytosis [...]Two men assigned to receive placebo were also terminated from the study early: one because a gastrointestinal tract malignancy was found and the other because he relocated." "1 patient was excluded (Baseline Testosterone Level Elevated)"	High rate of completion overall and per group. Details are provided regarding the participants terminated from the study
Incomplete data (safety outcomes)	Low	"One participant assigned to receive TRT was terminated from the study early because of treatment related erythrocytosis (hematocrit of 60% at 3-month visit), which resolved spontaneously within a few weeks of discontinuation of TRT. Two men assigned to receive placebo were also terminated from the study early: one because a gastrointestinal tract malignancy was found and the other because he relocated"	High rate of completion overall and per group. Details are provided regarding the participants terminated from the study.
Merza 2005	Judgment	Quote	Comment

Hackett 2013	Judgment	Quote	Comment
Sequence generation	Unclear	"The randomization list was generated by the Biostatistical Department at Ferring AB."	Sequence generation not described.
Allocation concealment	Unclear	"The randomization list was generated by the Biostatistical Department at Ferring AB."	Allocation concealment not described
Blinding (objective outcomes)	Low	"A randomized double-blind placebo-controlled study of 6 months testosterone or placebo patch therapy"	Blinding not well described, but not likely to have an effect on objective outcomes
Blinding (subjective outcomes)	Unclear	"A randomized double-blind placebo-controlled study of 6 months testosterone or placebo patch therapy"	Study was described as "double-blind" but blinding not described
Incomplete data (efficacy outcomes)	Low	Completion (RCT phase): placebo: 18/19 (95%); TRT: 20/20 (100%)	High completion rate, one missing patient not likely to have an impact on efficacy outcomes.
Incomplete data (safety outcomes)	Low	Completion (RCT phase): placebo: 18/19 (95%); TRT: 20/20 (100%) "In phase 1, one patient from the placebo group withdrew as he developed angina."	Only one withdrawal, reason stated (angina)
Brockenbrough 2006	Judgment	Quote	Comment
Sequence generation	Unclear	"Subjects were randomly assigned to administration of 100 mg of topical 1% testosterone gel or placebo for 6 months" "Block randomization was performed in groups of 4 according to baseline rHuEPO dose (≤ 250 or ≤ 250 /kg/wk) to minimize potential imbalance in rHuEPO doses between the treatment and control groups. Randomization was performed by a research pharmacist who was blinded to study medication type and was not involved in outcomes assessment"	Sequence generation not described beyond "blocked randomization"
Allocation concealment	Low	"Randomization was performed by a research pharmacist who was blinded to study medication type and was not involved in outcomes assessment"	Randomization was controlled by the pharmacy (pharmacist)
Blinding (objective outcomes)	Low	"This phase IV, single-center, placebo-controlled, doubleblind study assessed the effect of transdermal testosterone..."	Blinding not well described, but not likely to affect ROB for objective outcomes
Blinding (subjective outcomes)	Unclear	"This phase IV, single-center, placebo-controlled, double-blind study assessed the effect of transdermal testosterone..." "Subjects were randomly assigned to administration of 100 mg of topical 1% testosterone gel or placebo for 6 months. Testim 1% gel is manufactured by Auxilium Pharmaceuticals, which supplied the active and placebo gel used in this study. The gel was packaged in 5-g tubes, each of which delivered 50 mg of testosterone to the skin. Subjects were asked to apply 2 tubes of gel per day to the upper extremities for 6 months."	Blinding not well described
Incomplete data (efficacy outcomes)	High	Completion: Overall: 22/40 (55%); placebo: 12/19 (53%); TRT: 10/21 (57%) "Twenty-two subjects (55%) completed the 6-month protocol. Reasons for withdrawal from the placebo group included loss of interest in study participation (n=3), prolonged hospitalization (n=1), noncompliance (n=4), death caused by stroke (n=1), and renal transplantation (n=1). In the testosterone group, reasons for withdrawal included loss of interest (n=2), prolonged hospitalization (n=2), acne (n=1), and cardiovascular death (n=3)." "More of the study attrition (71%) in the testosterone group occurred in the first 3 months than in the placebo group (30%)" "Last observation carried forward was used in calculating mean hormone levels during the treatment period."	Although attrition and exclusions were reported, completion rates were < 80% in both arms. Authors state that LOCF was used but data appears to be based on completers (12 in placebo group, 10 in TRT group), the number of withdrawals totals 10 in the placebo group and 8 in the TRT group.
Incomplete data (safety)	Low	"Twenty-two subjects (55%) completed the 6-month protocol. Reasons for withdrawal from the placebo group included loss of	Denominators in reported in the safety table is looks as if

Hackett 2013	Judgment	Quote	Comment
outcomes)		interest in study participation (n=3), prolonged hospitalization (n=1), noncompliance (n=4), death caused by stroke (n=1), and renal transplantation (n=1). In the testosterone group, reasons for withdrawal included loss of interest (n=2), prolonged hospitalization (n=2), acne (n=1), and cardiovascular death (n=3).	all subjects were included in the safety analysis. All of the withdrawals were reported and accounted for.
Kuhnert 2005	Judgment	Quote	Comment
Sequence generation	Unclear	"Patients who met the inclusion criteria were assigned a randomisation number in ascending order. The randomization took place according to the biometrician's internal randomisation SOP. A randomisation list was generated by block randomisation with a specified block size of six units. Block size was not quoted in the protocol and not revealed to the investigators."	Sequence generation not described in sufficient detail
Allocation concealment	Low	As above	Allocation appears to be sufficiently concealed from investigators
Blinding (objective outcomes)	Low	"...a three-arm, parallel-group, open, randomised, controlled, multicentre, clinical trial"	Open-label as a result of the three products compared (scrotal gel, non-scrotal gel, arm patch); however, open design unlikely to affect objective outcomes
Blinding (subjective outcomes)	High	"...a three-arm, parallel-group, open, randomised, controlled, multicentre, clinical trial"	Open-label as a result of the three products compared (scrotal gel, non-scrotal gel, arm patch); potential high risk of bias for subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion: Patch: 30/52 (58%); non-scrotal gel: 40/56 (71%); scrotal gel: 41/54 (76%)	Completion rate varies by group. Data was analyzed based on the number of people who completed the first 12 weeks of treatment; reasons for withdrawal not well described (some people dropped out for "lack of treatment success")
Incomplete data (safety outcomes)	High	"Tolerability was significantly better in both gel groups than the patch group at every visit, judged by patients and physicians (P,0.01). In the gel groups, tolerability was assessed as 'very good' or 'good' in more than 92% of the patients, but in only 53.5% in the patch group. At weeks 20 and 24, none of the patients in the gel groups assessed tolerability as 'very poor' or 'poor', in contrast to 14-16% of the TTP group. The incidence of adverse events and severe adverse events not causally related to the medication did not differ significantly between groups. Significantly more skin reactions at the administration site were observed in the TTP group (13 patients) than in the scrotal or the dermal groups (two patients respectively) (one-sided U test; P,0.01). Six patients of the TTP group dropped out due to skin reactions, while no patient dropped out in either of the other groups for this reason. In the case of the patch application site, irritant reactions, erythema or pruritus were described. In the scrotal gel group, one patient also complained of pruritus after gel application and another of burning at the application site. One patient in the dermal group reported dryness at the application site, and another observed erythema when he did not remove the gel and perspired at the same time. These reactions disappeared spontaneously."	Safety outcomes were poorly reported and provided no usable data for our analysis
Orengo 2005	Judgment	Quote	Comment
Sequence generation	Low	"randomized through random number generation to receive either placebo or active T gel"	Judged low risk due to use of random number generator

Hackett 2013	Judgment	Quote	Comment
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"...received either placebo or active T gel"	Blinding not well described; however, not likely to introduce bias for objective outcomes
Blinding (subjective outcomes)	Unclear	"...received either placebo or active T gel"	Blinding not well described; insufficient to judge
Incomplete data (efficacy outcomes)	High	Completion: 12/18 = 67% Withdrawals are described but the numbers are not broken down by study group.	Judged high risk as completion rate is < 80%; analysis involved only on those who completed the study
Incomplete data (safety outcomes)	High	Total completion: 12/18 = 67% "Of the 6 participants who dropped out of the study, 3 had transportation difficulties, 1 moved out of state, and 2 had worsening of previous medical conditions" "No side effects were reported during the entire study and there were no medical complications."	Although 2 patients were described as withdrawing due to worsening of previous medical conditions they are not identified by study group and are not mentioned in the safety analysis
Schubert 2004	Judgment	Quote	Comment
Sequence generation	Low	"The patients were randomly assigned (using the SAS software)."	Computer-generated random numbers inferred by mention of SAS software
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"In an open-label, randomized, prospective trial, we investigated..."	Blinding not described, but trial described as open label. Not likely to introduce bias for objective outcomes
Blinding (subjective outcomes)	High	"In an open-label, randomized, prospective trial, we investigated..."	Open label trial
Incomplete data (efficacy outcomes)	Unclear	Completion: Nebido: 20/20 (100%); TE: 16/20 (80%)	Analysis is based on participants who completed 30 weeks of treatment.
Incomplete data (safety outcomes)	Low	Completion: Nebido: 20/20 (100%); TE: 16/20 (80%) "There were four dropouts during the main study (all from the TE group; three patients left the study for personal reasons and one patient was excluded because inclusion criteria had been violated)."	Completion % both above 80%; 4 people left from TE group, and reasons were stated for each.
Cavallini 2004	Judgment	Quote	Comment
Sequence generation	Unclear	"A total of 120 patients were randomized into three groups..."	Sequence generation not described
Allocation concealment	Unclear	"The drugs and placebo were given for 6 months, delivered by nurses unaware of the randomization group in anonymous color-coded boxes whose contents were disclosed at the end of the research"	Allocation concealment not sufficiently described
Blinding (objective outcomes)	Low	"The drugs and placebo were given for 6 months, delivered by nurses unaware of the randomization group in anonymous color-coded boxes whose contents were disclosed at the end of the research"	Blinding is not well described but is unlikely to have affected ROB for objective outcomes
Blinding (subjective outcomes)	Unclear	"The drugs and placebo were given for 6 months, delivered by nurses unaware of the randomization group in anonymous color-coded boxes whose contents were disclosed at the end of the research"	Blinding is not well described; unclear whether outcome assessors and patients were blinded

Hackett 2013	Judgment	Quote	Comment
		"The patients were randomized into three groups. The first group (40 patients, mean age 64 years, range 60 to 72) used testosterone undecanoate 160 mg/day. The second group (45 patients, mean age 66 years, range 61 to 73) used propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group (45 patients, mean age 63 years, range 61 to 74) received placebo (one 500-mg starch tablet/day)."	
Incomplete data (efficacy outcomes)	Unclear	Overall completion rate: 130/150= 87% "We enrolled 150 patients in the study; 20 subjects dropped out; and 130 subjects completed the protocol. The patients who withdrew were interviewed by telephone to ascertain the causes. Three patients indicated they did not get any benefit and refused to continue, 5 indicated they felt sufficiently better to discontinue, and 12 patients did not agree with the research because they had been informed they might have received a placebo. Their data were not used"	Completion rate in testosterone and placebo groups are unknown. Unclear as to of which participants dropped out from each group
Incomplete data (safety outcomes)	High	"The occurrence of side effects proved negligible with no statistically significant differences found among the three patient groups. In no patient was therapy suspended. One group 1 patient and one group 3 patient reported mild epigastralgia, and one group 2 patient reported mild headache." "We enrolled 150 patients in the study; 20 subjects dropped out; and 130 subjects completed the protocol."	Reasons were provided but not reported by group
Amory 2004	Judgment	Quote	Comment
Sequence generation	Low	"Participants were randomized by computer-generated assignment in permuted blocks of 6 to 1 of 3 treatment groups"	Computer-generated randomization
Allocation concealment	Low	"Only the research pharmacist and safety monitoring board knew the randomization assignment"	Looks to be pharmacy controlled
Blinding (objective outcomes)	Low	"We conducted a randomized, double-blind placebo-controlled trial..." "One of the investigators (N.B.W.) who was blinded to treatment analyzed all of the BMD measurements..." "The psychometrist was blinded to the participants' group membership."	Unclear whether the placebos were identical (two active treatments, double dummy); but unlikely to affect objective outcomes
Blinding (subjective outcomes)	Low	"We conducted a randomized, double-blind placebo-controlled trial..." "One of the investigators (N.B.W.) who was blinded to treatment analyzed all of the BMD measurements..." "The psychometrist was blinded to the participants' group membership." Participants were randomized to one of three treatment groups: 1) T-only group, T enanthate (TE; Schein Pharmaceuticals, Florham Park, NJ) 200 mg im every 2 wk, plus placebo pill orally [per os (po)] daily; 2) TF group, TE 200 mg im every 2 wk, plus F (Merck & Co., Rahway, NJ) 5 mg po daily; or 3) placebo group, sesame oil placebo 1 ml im every 2 wk, plus placebo pill po daily.	Double blind with a double dummy
Incomplete data (efficacy outcomes)	Unclear	Completion: Overall: 50/70 (71.4%%); TRT: 17/24 (70.8%); TRT+ Finasteride: 15/22 (68.2%; data not included for this group); placebo: 18/24 (75.0%) Companion: "At the 4-month evaluation, 65 men were available for testing, whereas 46 men completed the entire 36 months of the study. Of the 23 men who dropped out, 7 were in the T-only group and 8 each were in the T+F and placebo groups." "The primary analyses of the data were performed according to patients' original treatment assignment (i.e. intention-to-treat analyses), and all men were included in the analyses for as long as they contributed data" "Student's t tests were used to compare the pairwise differences between the model-based treatment means (least-squares means) at each time point or treatment month. The model-based means are unbiased with unbalanced and missing data, as long as the missing data are noninformative (missing at random). A dropout	Completion < 80%. Authors state ITT analysis, but description does not match ITT. Description of missing how they addressed missing data is unclear, and the number of participants who completed the trial is different between the parent and companion record.

Hackett 2013	Judgment	Quote	Comment
		process is assumed to be missing at random if, depending on the observed data, the dropout is independent of the unobserved measurements."	
Incomplete data (safety outcomes)	Unclear	"Of the 20 men who did not complete the study, six were in the placebo group, and seven each were in the T-only and T+F groups. Ten subjects dropped out of the study for personal reasons, and, as reported previously, three dropped out for prostate-related disease (one in the placebo group and two in the T-only group). The nonprostate intercurrent illnesses, which resulted in premature study cessation, were by treatment group and month of study cessation as follows: gastrointestinal bleeding (placebo, month 2); recurrent hematuria with negative workup (T-only, month 7); new onset atrial fibrillation (T-only, month 10); recurrence of old sciatica (T-only, month 14); adrenal cancer (T+F, month 5); appendicitis with peritonitis (T+F, month 7); and pancreatic cancer (T+F, month 16)." "For men who discontinued the study prematurely, telephone follow-up was conducted to ascertain clinical outcomes."	Parent (ID909) says 50 men completed 36 mo but companion (ID2330) states that 46 men completed 36 mo; we cannot resolve the missing men. Number of men randomized is also off by 1 man (in P group) between the two publications. We cannot determine which group the "personal reason" withdrawals were in
Tan 2003	Judgment	Quote	Comment
Sequence generation	Unclear	"Five patients were randomized to receive intramuscular testosterone enanthate 200mg every 2 weeks" "Five patients were randomized to receive a placebo" "Consecutive admissions to the nursing home were screened for Alzheimer's disease..."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"This was a randomized controlled study of testosterone versus placebo"	Blinding not well described; however, unlikely to affect objective outcomes
Blinding (subjective outcomes)	Unclear	"This was a randomized controlled study of testosterone versus placebo"	Blinding not well described
Incomplete data (efficacy outcomes)	Low	Completion: Overall: 9/10 (90%); placebo: 5/5 (100% completion); TRT: 4/5 (80%) completion to week 12	Completion data inferred based on the authors' reporting; unclear how missing data for 1 patient was addressed
Incomplete data (safety outcomes)	Low	"At the 9th month, one patient was dropped from the trial because he was exhibiting aggressive and hypersexual behavior, possibly secondary to the testosterone administration" "None of the five treated patients developed polycythemia or hyperlipidemia. Physical examination also did not reveal changes in prostate size, leg swelling, or breast enlargement."	Appears that only one participant withdrew from the study, with reason provided
Boyanov 2003	Judgment	Quote	Comment
Sequence generation	Unclear	"This study was an open-label, randomized, no-treatment controlled study..."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"open label" "subjects in the control group received no treatment"	Lack of blinding unlikely to affect objective outcomes
Blinding (subjective outcomes)	High	"open label" "subjects in the control group received no treatment"	Lack of placebo or blinding may affect subjective outcomes
Incomplete data (efficacy outcomes)	Low	"All subjects completed the study in accordance with the protocol."	Judged low risk as all participants appeared to be included in the analysis
Incomplete data (safety)	Low	"All subjects completed the study in accordance with the protocol."	Judged low risk as all participants appeared to

Hackett 2013	Judgment	Quote	Comment
outcomes)			have completed the study
Steidle 2003	Judgment	Quote	Comment
Sequence generation	Unclear	"The study was designed as a randomized, multidose, multicenter, active, and placebo-controlled study" "Randomization was performed to ensure an equal distribution of treatments across study centers"	No information provided with which to make assessment
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"The AA2500 and placebo gel were identical and applied as two tubes of 50 mg T (100 mg/d), one tube of 50 mg T and one tube of placebo (50 mg/d), or two tubes of placebo. Neither the patients nor the investigators were aware of the contents of the tubes." "The study was double blinded for the AA2500 and placebo groups and open label for the T patch group"	Open label for one treatment but not likely to influence objective outcomes
Blinding (subjective outcomes)	High	"The AA2500 and placebo gel were identical and applied as two tubes of 50 mg T (100 mg/d), one tube of 50 mg T and one tube of placebo (50 mg/d), or two tubes of placebo. Neither the patients nor the investigators were aware of the contents of the tubes." "The study was double blinded for the AA2500 and placebo groups and open label for the T patch group"	Trial was only partly blinded (two gel arms were blinded; patch arm was open)
Incomplete data (efficacy outcomes)	High	"A significant proportion of enrolled patients completed the 90-d study (90% and 92% in the AA2500 and placebo groups respectively and 75% in the T patch group).	Completion rate is misleading because it combines the 50-mg and 100-mg dose groups. At day 90, there were 45 patients (of 99; 45% completion) in the 50-mg gel group, 105 (of 106) in the 100-mg group (43 switched into this group at day 60), 60 patients (of 102; 59%) in the patch group, and 80 (of 99; 81%) in the placebo group.
Incomplete data (safety outcomes)	High	"The primary reason for the higher rate of discontinuations in the T patch group was adverse events (17%) with the majority of events being related to skin irritations at the patch site." "Only six patients in AA2500 treatment groups experienced adverse events that led to discontinuation. Specific events in the 100 mg/d AA2500 treatment group included vertigo, coronary artery disease, depression with suicidal ideation, urinary tract infection/pneumonia, and hypertension. All events with the exception of hypertension were considered unrelated to treatment. Mood swings, considered related to treatment, was the only event in the 50 mg/d AA2500 treatment group that led to discontinuation."	Incomplete reporting of data. Although some losses to adverse events are mentioned, there is not a complete accounting of withdrawals
McNicholas 2003	Judgment	Quote	Comment
Sequence generation	Unclear	NR	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"The Testim treatments were double-blinded by using a matched placebo gel but was open-label for the Andropatch group." "The study was designed as a randomized, multidose, multicentre, active controlled study"	Blinding not well described, but unlikely to affect objective outcomes
Blinding (subjective outcomes)	High	"The Testim treatments were double-blinded by using a matched placebo gel but was open-label for the Andropatch group." "The study was designed as a randomized, multidose, multicentre, active controlled study"	Blinding not well described; may affect subjective outcomes. Open label for patch group

Hackett 2013	Judgment	Quote	Comment
Incomplete data (efficacy outcomes)	High	93% completed the Testim 50 mg/d arm, 97% completed the Testim 100% group. Reasons for attrition not clearly stated "most being related to skin irritation at the patch site" 79% completed the Androderm arm	Number of discontinuations varied by group; unclear how patients who switched treatments are accounted for
Incomplete data (safety outcomes)	High	"Overall, the incidence of experiencing one or more treatment-emergent adverse events was similar in the Testim groups, but was about twice as high in the Andropatch group, at 35% for 50 and 29% for 100 mg/day Testim, and 63% for the Andropatch." "Whilst treatment in the Testim groups was relatively well-tolerated over the 90-day period, the Andropatch treated men had a substantially higher rate of adverse events."	Reasons for discontinuation not well described, with a lot of variation in rates of loss between groups
Ferrando 2002	Judgment	Quote	Comment
Sequence generation	Unclear	"Twelve healthy older men were randomly assigned in double-blind fashion to receive either testosterone enanthate (TE) or placebo for 6 months."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"Twelve healthy older men were randomly assigned in double-blind fashion to receive either testosterone enanthate (TE) or placebo for 6 months." "...placebo consisting of sesame seed oil." "TE injections were adjusted by an independent clinician (every 2 wk) to maintain levels within the normal range."	Blinding not well described, but unlikely to influence objective outcomes
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest; no safety reported but all appeared to have completed the trial.
Incomplete data (efficacy outcomes)	Low	Inferred: all participants completed the trial (individual measurements for all TRT-treated participants); reporting was less clear for the placebo group; however, the authors state that "5 subjects who received placebo demonstrated no change throughout the study in IGF 1", suggesting that all placebo participants also completed the trial	All participants appeared to have completed the trial
Incomplete data (safety outcomes)	Low	Inferred: all participants completed the trial (individual measurements for all TRT-treated participants); reporting was less clear for the placebo group; however, the authors state that "5 subjects who received placebo demonstrated no change throughout the study in IGF 1", suggesting that all placebo participants also completed the trial	All participants appeared to have completed the trial
Kang 2002	Judgment	Quote	Comment
Sequence generation	Unclear	"Thirty-five men (aged 58 +/- 8 years) with CAD were randomized to placebo (n = 17) or treatment group (n = 18)."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"Thirty-five men (aged 58 +/- 8 years) with CAD were randomized to placebo (n = 17) or treatment group (n = 18)."	Blinding not described; however, unlikely to affect objective outcomes
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Low	It appears as if all patients completed the trial. Testosterone levels were reported for all subjects randomized.	Judged low ROB because outcome data were available for all patients randomized
Incomplete data (safety)	Low	It appears as if all patients completed the trial. Testosterone levels were reported for all subjects randomized.	No safety outcomes reported but all participants

Hackett 2013	Judgment	Quote	Comment
outcomes)			appeared to have completed the trial
Simon 2001	Judgment	Quote	Comment
Sequence generation	Unclear	"The 18 selected men were randomly assigned to one of three treatment groups..."	Sequence generation not described
Allocation concealment	Unclear	"The randomization code was known only to the study manager."	Allocation concealment not reported in sufficient detail
Blinding (objective outcomes)	Low	"To maintain the double blinding, the study manager also sometimes changed the dose of placebo." "For hormone measurements at baseline and at the end of the trial ... all of the analysts were blind to the treatment allocation."	Blinding is adequate for objective outcomes
Blinding (subjective outcomes)	Low	"The 18 selected men were randomly assigned to one of three treatment groups testosterone, DHT or placebo. The randomization code was known only to the study manager. Treatment was a gel administered every morning by percutaneous route." "To maintain the double blinding, the study manager also sometimes changed the dose of placebo." "For hormone measurements at baseline and at the end of the trial ... all of the analysts were blind to the treatment allocation." (However this quote may not be relevant to the only usable safety outcome which is below.) "The only serious event was the discovery of a prostatic nodular hyperplasia benign at biopsy, in a subject treated by testosterone."	Method of blinding was described and sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	NA	NA	No efficacy outcomes of interest
Incomplete data (safety outcomes)	Low	"The only missing datum was one 2-h plasma insulin measurement at 3 months in a subject treated by DHT."	All patients appear to have completed the trial
Wang 2000	Judgment	Quote	Comment
Sequence generation	Unclear	"The study was a randomized multicentre (16 centres), parallel study..."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"The study was double blind with respect to the T gel dose and open label for the T patch group."	Partially blinding is unlikely to influence objective outcomes
Blinding (subjective outcomes)	High	"The study was double blind with respect to the T gel dose and open label for the T patch group."	Incomplete blinding could affect subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion: Overall: 195/227 (86%); Androderm 5 mg: 55/76 (72%); Androgel 50 mg: 68/73(93%); Androgel 100 mg: 72/78 (92%) "Two hundred and twenty-seven subjects were initially randomized to 73 in the T gel 50 mg/day (in 5 g gel), 78 in the T gel 100 mg/day (in 10 g gel), and 76 in the T patch groups, respectively. At 90 days, dose adjustments were made in the T gel groups based on the preapplication serum T levels on day 60. Twenty subjects in the 50 mg/day T gel group had the T gel dose increased to 75 mg/day, and 20 in the T gel 100 mg/day group had the T gel dose reduced to 75 mg/day. There were 3 patients in the T patch group who were switched to 50 mg/day T gel because of patch intolerance, one 100 mg/day T gel subject was adjusted to receive 50 mg/day, and one 50 mg/day T gel subject had the dose adjusted to 25 mg/day. The number of subjects enrolled in days 91–180 of the study consisted of 51 continuing 50 mg/ day T gel, 40 receiving 75 mg/day T gel, 52 receiving 100 mg/day T gel, and	High overall completion rate; however, high there is a differential between groups. Handling of missing data and crossovers is not addressed. Completion rate reflects the patients who continued into the second phase of the study and might not be the same as those who were assessed for the 90 day outcomes.

Hackett 2013	Judgment	Quote	Comment
		52 continuing on the patch."	
Incomplete data (safety outcomes)	High	As above	The study does not provide a complete description of all patients withdrawn or the handling of crossovers; denominators used in safety analysis are not reported.
Bhasin 2000	Judgment	Quote	Comment
Sequence generation	Low	"Using randomization schedules, generated to create random numbers from a uniform distribution on unit interval, 61 eligible men were assigned to 1 of 4 groups."	Judged low risk as random number generation was described.
Allocation concealment	Unclear	NR	Allocation concealment not described
Blinding (objective outcomes)	Low	"Placebo-controlled, double-blind, randomized clinical trial...". Placebo group received injections of sesame oil.	Blinding not well described, but unlikely affect objective outcomes
Blinding (subjective outcomes)	Unclear	"Double blind". Placebo group received injections of sesame oil.	No description of blinding method provided. Judged unclear as ineffective blinding could bias patients self report of subjective outcomes.
Incomplete data (efficacy outcomes)	Low	Completion Rate: 49/61 80% PI: 23/29 = 79% T: 26/32 = 81% "For secondary variables (ie testosterone levels), the last values carried forward for withdrawn patients were analyzed." However at the bottom of Table 2 in which the results for T levels are reported the article states that "the data represent the mean (SEM) of all available values on that day. However, the change represents the difference between paired values only."	Overall completion rate is about 80% and similar between groups
Incomplete data (safety outcomes)	Unclear	No reporting of the number of participants included in the safety analysis. Reasons for withdrawal are not reported.	Reasons for withdrawal not reported; insufficient information with which to judge ROB
Dobs 1999	Judgment	Quote	Comment
Sequence generation	Unclear	Qualified patients were randomized in an age-matched fashion to treatment with either TTD or IM therapy for 24 weeks.	Sequence generation not described.
Allocation concealment	Low	"The randomization was done centrally by the sponsor."	Judged low risk as allocation was central in a multicenter trial
Blinding (objective outcomes)	Low	"open label" "examiners were also not blind to treatment"	Lack of blinding would be unlikely to affect testosterone levels
Blinding (subjective outcomes)	High	"open label" "because patients were aware of the type of treatment they received some bias in the subjective assessment was possible" "examiners were also not blind to treatment"	Lack of blinding could affect the subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion rate: Overall: 58/66 = 88% Androderm: 26/33 = 78% Delatestryl: 32/33 = 97%	Although the overall completion rate was high the completion rate in the Androderm group was < 80% and was lower than that in the Delatestryl group. This was primarily due to a higher number of withdrawals due to adverse events for Androderm.

Hackett 2013	Judgment	Quote	Comment
			There is no description in the article regarding the handling of missing data or any mention of ITT. The Ns analyzed for most outcomes are lower than the number of patients who completed the study and in several instances are below 80%.
Incomplete data (safety outcomes)	Unclear	5 of the 8 withdrawals from the study were due to adverse events, 4 of which were in the Androderm group and one in Delatestryl. The other 3 patients withdrew from Androderm for "personal reasons". The adverse events in the TTD group included depression (one patient), allergic contact dermatitis to the TTD (two patients), and local intolerance to the TTD associated with erythema and pruritus (one patient). One IM-treated patient reporting depression, fatigue, edema, weight gain, shortness of breath, joint pain, headaches, and muscular pain withdrew from the study. Three patients in the TTD group withdrew for personal reasons. Overall, 26 patients in the TTD group and 32 patients in the IM group completed the study.	The completion rate was > 80%; however, personal reasons varied between groups and are not well described
Clague 1999	Judgment	Quote	Comment
Sequence generation	Unclear	"In this double blind placebo controlled study, subjects were randomly allocated to treatment with testosterone enanthate 200 mg i.m. (Schering Health Care Ltd) or placebo (castor oil) at 2 weekly intervals."	Sequence generation not reported
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"'Blind' preparations were produced by the Pharmacy Department at Withington Hospital, Manchester, and given by one of the investigators (JEC)."	Judged to be as low risk of bias for objective outcomes because placebo was masked
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Low	"In total, 85 subjects were screened to identify suitable healthy older subjects. Results from a preliminary analysis of 14 subjects recruited from this group are presented. All met the inclusion criteria and all completed the study."	Completion 100%
Incomplete data (safety outcomes)	Low	"All met the inclusion criteria and all completed the study."	Completion 100%
Bhasin 1998	Judgment	Quote	Comment
Sequence generation	Unclear	"Patients fulfilling the inclusion criteria were randomly assigned to one of two treatment groups"	Sequence generation not reported
Allocation concealment	Unclear	NA	Allocation concealment not reported
Blinding (objective outcomes)	Low	"This was a single centre, double blind, placebo controlled randomized study..."	Blinding not described beyond "double blind" but not judged to affect ROB for objective outcomes
Blinding (subjective outcomes)	Unclear	"This was a single centre, double blind, placebo controlled randomized study..."	Insufficient detail to assess how blinding may have affected ROB for subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion: Overall: 32/41 (78.0%); Testosterone: 14/20 (70.0%); Placebo: 18/21 (85.7%) "One participant in the testosterone group withdrew because of	Completion varied considerably across the treatment arms. Analysis was based on participants

Hackett 2013	Judgment	Quote	Comment
		adverse experience (suicidal drug overdose). Three men in the placebo group and 5 in the testosterone group were lost to follow-up or discontinued treatment due to nonstudy-related personal reasons or failure to comply with the protocol. Three men withdrew in the first 15 days of the treatment period; 6 additional men withdrew before completing 10 weeks of treatment."	who completed the study.
Incomplete data (safety outcomes)	Unclear	Completion: Overall: 32/41 (78.0%); Testosterone: 14/20 (70.0%); Placebo: 18/21 (85.7%) "One participant in the testosterone group withdrew because of adverse experience (suicidal drug overdose). Three men in the placebo group and 5 in the testosterone group were lost to follow-up or discontinued treatment due to nonstudy-related personal reasons or failure to comply with the protocol. Three men withdrew in the first 15 days of the treatment period; 6 additional men withdrew before completing 10 weeks of treatment."	All participants are accounted for; however, reasons for discontinuation were not adequately described (don't know how many in the 8 non-AE withdrawals were lost to follow or failure to comply with protocol - which may have been tolerability related)
Grinspoon 1998	Judgment	Quote	Comment
Sequence generation	Low	"A Randomized, Double-Blind, Placebo-Controlled Trial" "Patients were randomly assigned to receive testosterone enanthate, 300 mg (Bio-Technology General Corp., Iselin, NJ), or placebo intramuscularly every 3 weeks by self-injection. Participants were stratified for weight less than or greater than 90% of ideal body weight and megestrol acetate use before randomization. Randomization was performed by the Massachusetts General Hospital Pharmacy by using a permuted block algorithm. The correspondence between patient code number and drug was generated by the study statistician. This list was available to the hospital pharmacist but not to the investigators or patients".	Permuted block algorithm judged to be sufficient for low ROB
Allocation concealment	Low	"The correspondence between patient code number and drug was generated by the study statistician. This list was available to the hospital pharmacist but not to the investigators or patients".	Central allocation judged to be sufficient for low ROB
Blinding (objective outcomes)	Low	"A Randomized, Double-Blind, Placebo-Controlled Trial" "The correspondence between patient code number and drug was generated by the study statistician. This list was available to the hospital pharmacist but not to the investigators or patients" "The placebo contained sesame oil with chlorobutanol as a preservative and matched testosterone enanthate in color and consistency"	Patients and investigators were blinded as to treatment assignment
Blinding (subjective outcomes)	Low	As above	Patients and investigators were blinded as to treatment assignment
Incomplete data (efficacy outcomes)	High	Completion: 22/26 in T arm (85%); 19/26 (76%) in placebo arm. Overall: 79% "Forty-one patients completed the protocol. No follow-up data were available from eight patients. Partial follow-up data were available from two patients. In this model, we compared the change from baseline at 6 months in the two treatment groups while controlling for the baseline value. We used a Mest to compare patient reports of response to therapy at 6 months between the groups. Patients were classified according to whether they were receiving protease inhibitors at baseline, started receiving them during the study, or never received them. We used the Fisher exact test to compare the proportions in these three groups between the two treatment and to compare survival between groups. To ensure that the differences in the primary end points were not biased by mortality, we did a secondary analysis	Completion rate < 80% and variable between arms, and method of addressing missing data not reported.

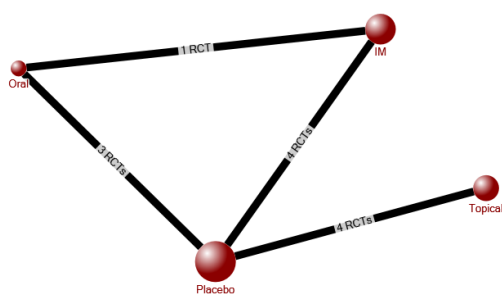
Hackett 2013	Judgment	Quote	Comment
		that combined mortality and body composition. In the combined analysis, we classified deaths as having an extreme decrease in mass, then used a Wilcoxon test to compare the groups." "The treatment effect over 6 months was estimated by analysis of covariance with all observations available from each patient in an intention-to-treat analysis."	
Incomplete data (safety outcomes)	Unclear	"Seven patients died of AIDS-related complications before completing the study (three in the testosterone group and four in the placebo group)." "Two patients (one in each group) dropped out of the study for personal reasons. One additional patient was withdrawn from the study at baseline before initiation of therapy because of gastrointestinal bleeding. No patient withdrew from the study because of a drug-related side effect. Prostate enlargement or new nodules were not detected in any patient."	Number of withdrawals was similar between groups. All withdrawals accounted for; however, personal reasons not well described
Jockenhovel 1997, p. 2510	Judgment	Quote	Comment
Sequence generation	Unclear	"In this single center study 22 men with hypogonadism ... were randomly assigned ..."	Sequence generation not described
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"were randomly assigned to T enanthate (TE; Testoviron depot 250, Schering, Berlin, Germany) or T pellets (TPEL), a single sc implantation of 6 testosterone pellets each containing 200 mg crystalline T"	Blinding not reported; however, objective outcome (testosterone level) was unlikely be influenced by a lack of blinding
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data (efficacy outcomes)	Unclear	There was no mention of attrition, exclusions, discontinuations, withdrawals or participants lost to follow-up.	22 men randomized; no mention of completion or dropouts. No mention of how complete the outcome data was or how missing data was dealt with.
Incomplete data (safety outcomes)	Unclear	There was no mention of attrition, exclusions, discontinuations, withdrawals or participants lost to follow-up.	22 men randomized; no mention of completion or dropouts. No mention of how complete the outcome data was or how missing data was dealt with.
Jockenhovel 1997, p. 293	Judgment	Quote	Comment
Sequence generation	Unclear	"In an open label study patients with clinically and biochemical confirmed androgen deficiency (serum testosterone <3.6 nmol/L on at least 2 occasions) were randomized to 1 of 4 treatment protocols"	Sequence generation not reported
Allocation concealment	Unclear	"In an open label study patients with clinically and biochemical confirmed androgen deficiency (serum testosterone <3.6 nmol/L on at least 2 occasions) were randomized to 1 of 4 treatment protocols"	Allocation concealment not reported
Blinding (objective outcomes)	Low	"...open label study..."	Open label design not likely to bias objective outcomes
Blinding (subjective outcomes)	NA	NA	No subjective outcomes of interest
Incomplete data	Unclear	There was no mention of attrition, exclusions, discontinuations,	

Hackett 2013	Judgment	Quote	Comment
(efficacy outcomes)		withdrawals or participants lost to follow-up.	
Incomplete data (safety outcomes)	Unclear	There was no mention of attrition, exclusions, discontinuations, withdrawals or participants lost to follow-up.	
Sih 1997	Judgment	Quote	Comment
Sequence generation	Low	"Subjects were assigned by random number to the treatment or control group."	Randomization not well reported, but use of random numbers is sufficient for "low" ROB rating
Allocation concealment	Unclear	NR	Allocation concealment not reported
Blinding (objective outcomes)	Low	"The treatment group received 200 mg (1 ml) testosterone cypionate IM every 14–17 days for 12 months. Those in the control group received 1 ml normal saline IM every 14–17 days for 12 months. Injections were administered by a physician or a nurse in the clinic. Subjects and technicians performing the assays were blind about which treatment was given"	Blinding sufficient for objective outcomes
Blinding (subjective outcomes)	Unclear	"The treatment group received 200 mg (1 ml) testosterone cypionate IM every 14–17 days for 12 months. Those in the control group received 1 ml normal saline IM every 14–17 days for 12 months. Injections were administered by a physician or a nurse in the clinic. Subjects and technicians performing the assays were blind about which treatment was given"	Blinding sufficient for subjective outcomes
Incomplete data (efficacy outcomes)	High	Completion: TRT: 10/17 (59%); control: 12/15 (80%)	Testosterone levels at each time point base on the number of people remaining in the trial at that time. Attrition not balanced between groups.
Incomplete data (safety outcomes)	Unclear	"Seventeen subjects entered the treatment group; one withdrew due to lymphoma prior to the 3 month evaluation; one withdrew because of uncontrolled atrial fibrillation with congestive heart failure, one was lost to follow-up before the 6-month evaluation; one was lost to follow-up, and three withdrew because of increases in hematocrit before the 9-month evaluation. Fifteen men entered the control group: one was lost to follow up before the 3-month evaluation; one withdrew because of a stroke, and one was lost to follow-up before the 9-month evaluation."	Safety analysis based on the number of participants randomized. Attrition reported but reasons not provided for loss to follow-up

APPENDIX 6: EVALUATION OF NETWORK CONSISTENCY

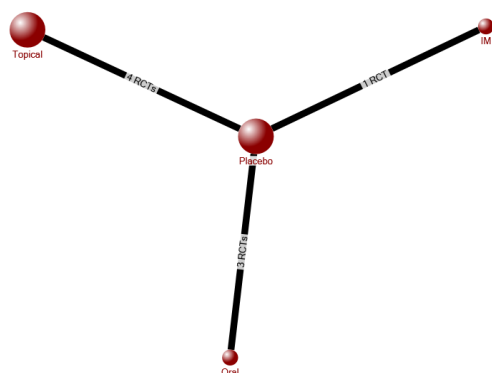
One of the key assumptions in network meta-analysis is that estimates derived from indirect comparisons are consistent with those from direct comparisons. We evaluated the consistency of the network for networks with closed loops. To be classified as a “closed loop,” the nodes had to be connected by more than one RCT (e.g., not connected solely by a multi-arm trial). For example, in the following network, the loop between oral testosterone, intramuscular testosterone, and placebo is informed by multiple RCTs, and consistency of the evidence can be evaluated.

FIGURE: EXAMPLE OF A CLOSED LOOP IN AN EVIDENCE NETWORK.



In contrast, the consistency cannot be evaluated if no closed loops are present, such as in the following example.

FIGURE: EXAMPLE OF A NETWORK WITH NO CLOSED LOOPS

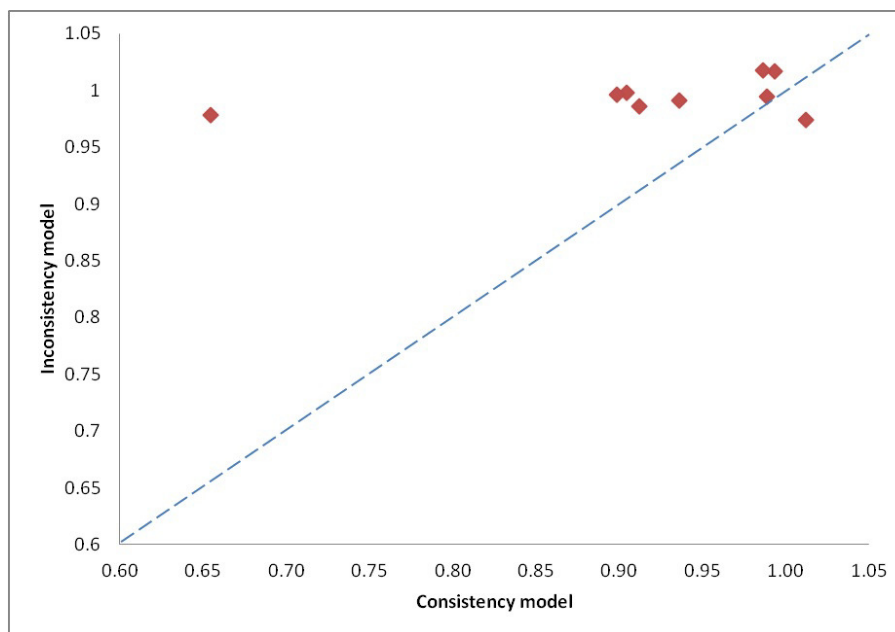


To evaluate the consistency of networks with closed loops, two analyses were performed. One was conducted using the standard consistency model (this model was used for the

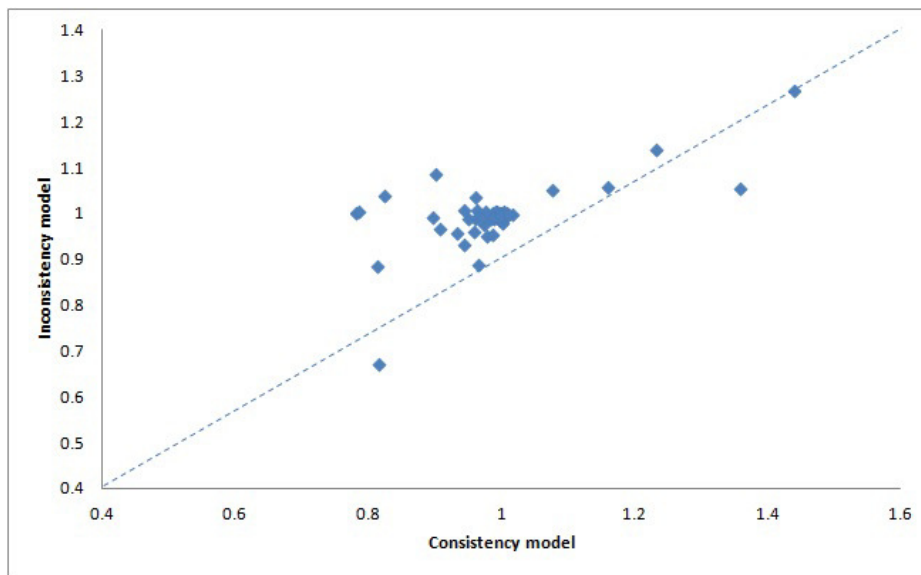
primary analyses), which assumes that the data in the network are consistent. A second analysis was performed using an inconsistency model, which assumes that the data in the network are not consistent. To identify the presence of inconsistency, the posterior mean deviance of the individual data points derived from the inconsistency model was plotted against the posterior mean deviance derived from the consistency model. If the network is consistent, most of the data points will lie along the diagonal line indicating that the estimates are similar from both models. If inconsistency is present, data points will lie in the under the diagonal line, indicating a deviation from the consistency model. Data points above the diagonal line indicate deviation from the inconsistency model and are not indicative of inconsistency.

Model fit can also be evaluated by considering the residual deviance and DIC of the inconsistency and consistency models, with the model that has the lower residual deviance and DIC representing the better fit for the data. In the present study, the consistency model had a lower residual deviance and DIC for each outcome, thus representing a better fit.

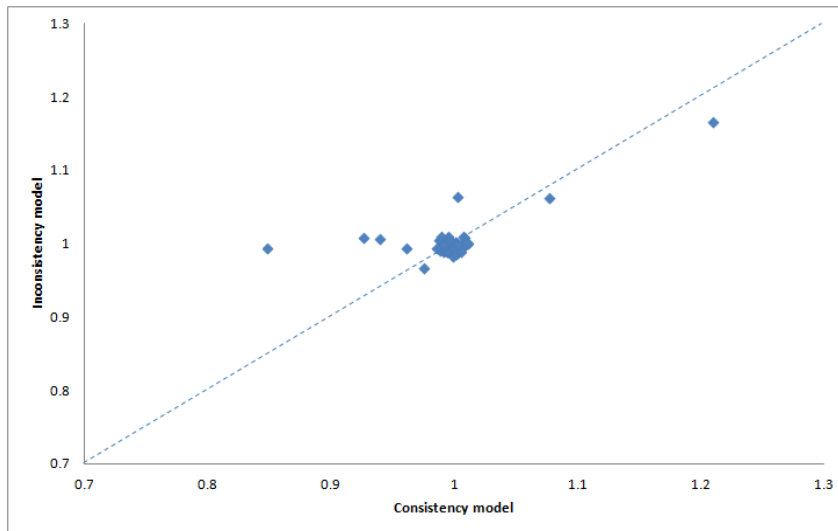
LIBIDO: BASE CASE (ALL STUDIES)



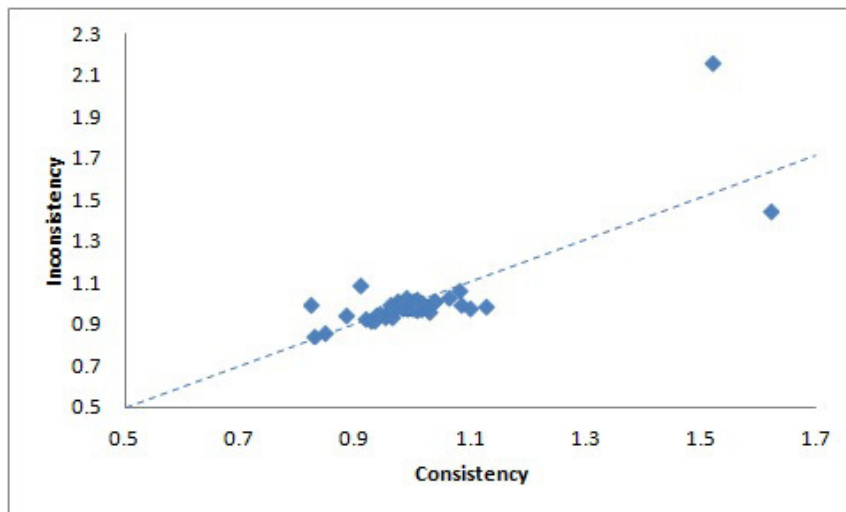
TOTAL TESTOSTERONE LEVEL, 3 MO



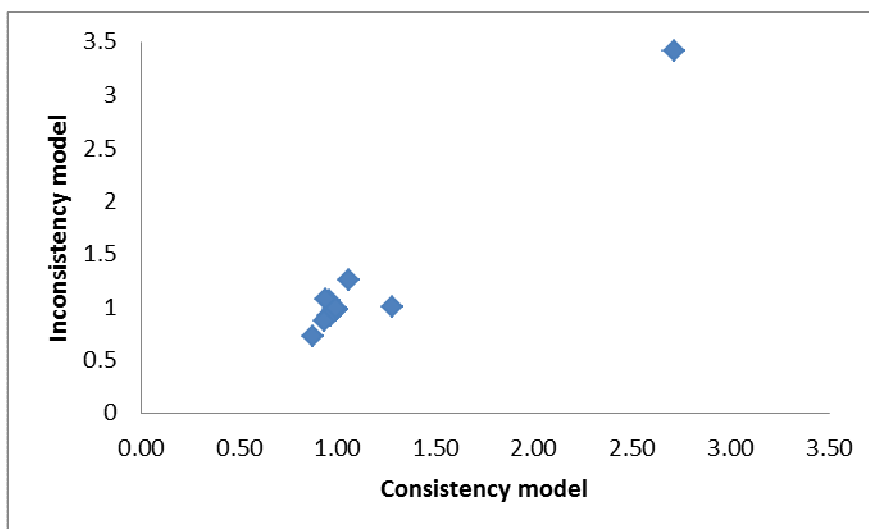
TOTAL TESTOSTERONE LEVEL, 6 MO



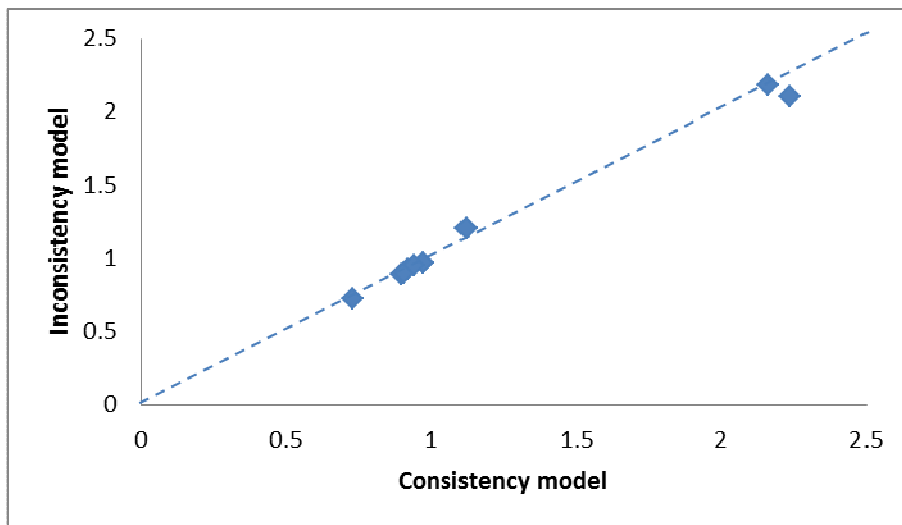
TOTAL TESTOSTERONE LEVEL, END OF STUDY



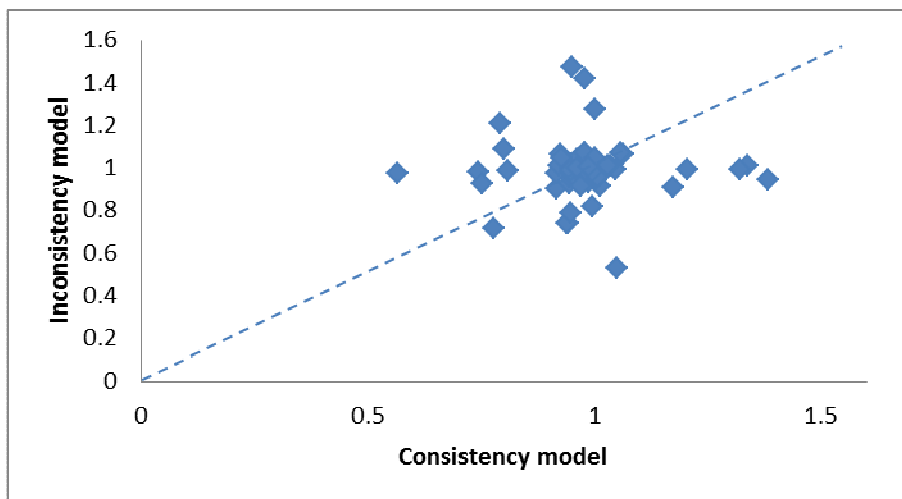
QUALITY OF LIFE, BY ROUTE OF ADMINISTRATION



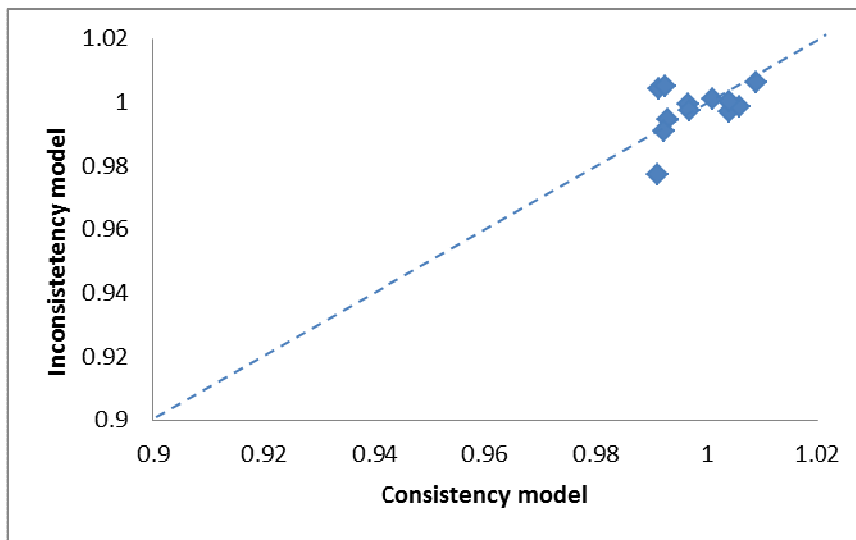
ERECTILE FUNCTION, BY ROUTE OF ADMINISTRATION



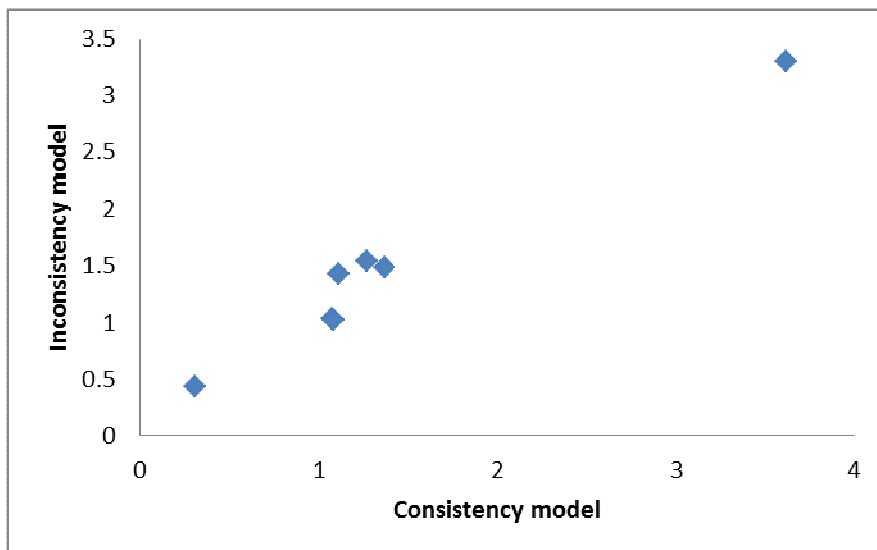
TESTOSTERONE LEVEL, BY ROUTE OF ADMINISTRATION



QUALITY OF LIFE, TREATMENT DURATION AT LEAST 6 MO



LIBIDO, TREATMENT DURATION LESS THAN 6 MO



APPENDIX 7: INCLUDED NON-RANDOMIZED STUDIES OF INTERVENTIONS

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol*. 2005;173 (2):533-536.
2. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol*. 2009;53 (8):996-1004.
3. Arafa M, Zohdy W, Aboulsoud S, Shamloul R. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia*. 2012;44 Suppl 1:756-763.
4. Aversa A, Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 36 months controlled study. *Aging Male*. 2012;15 (2):96-102.
5. Aydogdu A, Bolu E, Sonmez A, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clinical Endocrinology*. 79 (2) (pp 243-251), 2013. Date of Publication: August 2013. 2013 (2):243-251.
6. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? *BJU International*. 2004;94 (7):1066-1070.
7. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. *Postgrad.Med*. 2013;125 (2):30-39.
8. Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of testim(r) 1% testosterone gel in hypogonadal men. *Rev. 2005;urol.* 7 (2):87-94.
9. Francomano D, Bruzziches R, Barbaro G, Lenzi A, Aversa A. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: A pilot study. *Journal of Endocrinological Investigation*. 37 (4) (pp 401-411), 2014. Date of Publication: April 2014. 2014 (4):401-411.
10. Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology*. 2014;83 (1):167-173.
11. Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *International Journal of Endocrinology*. 2014 , 2014. Article Number: 527470. Date of Publication: 2014. 2014.
12. Gooren LJ, Saad F, Haide A, Yassin A. Decline of plasma Salpha-dihydrotestosterone (DHT) levels upon testosterone administration to elderly men with subnormal plasma testosterone and high DHT levels. *Andrologia*. 2008;40 (5):298-302.
13. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. *Endocr.Pract*. 2000;6 (2):132-138.
14. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *Journal of Clinical Endocrinology and Metabolism*. 1997;82 (11):3793-3796.
15. Host C, Bojesen A, Frystyk J, Flyvbjerg A, Christiansen JS, Gravholt CH. Effect of sex hormone treatment on circulating adiponectin and subforms in Turner and Klinefelter syndrome. *European Journal of Clinical Investigation*. 40 (3) (pp 211-219), 2010. Date of Publication: March 2010. 2010 (3):211-219.
16. Jin B, Conway AJ, Handelsman DJ. Effects of androgen deficiency and replacement on prostate zonal volumes. *Clinical Endocrinology*. 54 (4) (pp 437-445), 2001. Date of Publication: 2001. 2001 (4):437-445.
17. Kacker R, Connors W, Zade J, Morgentaler A. Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. *Journal of Urology*. 191 (4) (pp 1072-1076), 2014. Date of Publication: April 2014. 2014 (4):1072-1076.
18. Kalinchenko S, Vishnevskiy EL, Koval AN, Mskhalaya GJ, Saad F. Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: A pilot study. *Aging Male*. 2008;11 (2):57-61.
19. Kubler A, Schulz G, Cordes U, Beyer J, Krause U. The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Experimental and Clinical Endocrinology*. 100 (3) (pp 129-132), 1992. Date of Publication: 1992. 1992 (3):129-132.
20. La VS, Calogero AE, D'Agata R, et al. Testosterone therapy improves the clinical response to conventional treatment for male patients with metabolic syndrome associated to late onset hypogonadism. *Minerva Endocrinologica*. 2008;33 (3):159-167.
21. La VS, Condorelli R, Vicari E, D'Agata R, Calogero A. Original immunophenotype of blood endothelial progenitor cells and microparticles in patients with isolated arterial erectile dysfunction and late onset hypogonadism: Effects of

- androgen replacement therapy. *Aging Male*.14 (3) (pp 183-189), 2011.Date of Publication: September 2011. 2011 (3):183-189.
22. McCullough AR, Khera M, Goldstein I, Hellstrom WJ, Morgentaler A, Levine LA. A multi-institutional observational study of testosterone levels after testosterone pellet (Testopel()) insertion. *J Sex Med*. 2012;9 (2):594-601.
 23. Morgunov LI, Denisova IA, Rozhkova TI, Stakhovskaia LV, Skvortsova VI. Androgenic deficit and its treatment in stroke male patients with diabetes mellitus type II. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2011;111 (8 Pt 2):21-24.
 24. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur. J. ENDOCRINOL.* 169 (6):725-733.
 25. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. *Aging Male*. 2003;6 (2):86-93.
 26. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. *International Journal of Impotence Research*.18 (2) (pp 201-205), 2006.Date of Publication: March 2006. 2006 (2):201-205.
 27. Ross RJM, Siyambalapitiya S, Jonsson P, Koltowska-Haggstrom M, Gaillard R, Ho K. Cross-sectional analysis of testosterone therapies in hypopituitary men on stable pituitary hormone replacement. *Clinical Endocrinology*.70 (6) (pp 907-913), 2009.Date of Publication: June 2009. 2009 (6):907-913.
 28. Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. *J Androl*. 2008;29 (1):102-105.
 29. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *Journal of Clinical Endocrinology and Metabolism*. 2012;97 (6):2050-2058.
 30. Strollo F, Strollo G, More M, et al. Low-intermediate dose testosterone replacement therapy by different pharmaceutical preparations improves frailty score in elderly hypogonadal hyperglycaemic patients. *Aging Male*. 2013;16 (2):33-37.
 31. Swerdloff RS, Wang C. Three-year follow-up of androgen treatment in hypogonadal men: preliminary report with testosterone gel. *Aging Male*. 2003;6 (3):207-211.
 32. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: Efficacy and treatment cost. *Journal of Sexual Medicine*.7 (1 PART 1) (pp 269-276), 2010.Date of Publication: January 2010. 2010 (1 PART 1):269-276.
 33. Thomson S, Koren G, Van SV, Rieder M, Van Uum SHM. Testosterone concentrations in hair of hypogonadal men with and without testosterone replacement therapy. *Therapeutic Drug Monitoring*.31 (6) (pp 779-782), 2009.Date of Publication: December 2009. 2009 (6):779-782.
 34. Trabado S, Maione L, Bry-Gaillard H, et al. Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/kallmann syndrome and effects of different modalities of hormonal treatment: A single-center study of 281 patients. *Journal of Clinical Endocrinology and Metabolism*.99 (2) (pp E268-E275), 2014.Date of Publication: February 2014. 2014 (2):E268-E275.
 35. Trabado S, Maione L, Salenave S, et al. Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities of hormonal treatment. *Fertility and Sterility*.95 (7) (pp 2324-2329.e3), 2011.Date of Publication: June 2011. 2011 (7):2324-2329.
 36. van den Bergh JP, Hermus AR, Spruyt AI, Sweep CG, Corstens FH, Smals AG. Bone mineral density and quantitative ultrasound parameters in patients with Klinefelter's syndrome after long-term testosterone substitution. *Osteoporos.Int*. 2001;12 (1):55-62.
 37. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA : the journal of the American Medical Association*. 2013;310 (17):1829-1836.
 38. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism*. 2004;89 (5):2085-2098.
 39. Yaron M, Greenman Y, Rosenfeld JB, et al. Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. *Eur J Endocrinol*. 2009;160 (5):839-846.
 40. Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E. Prostate volume and growth in testosterone-substituted hypogonadal men are dependent on the CAG repeat polymorphism of the androgen receptor gene: a longitudinal pharmacogenetic study. *Journal of Clinical Endocrinology and Metabolism*. 2003;88 (5):2049-2054.

APPENDIX 8: ODDS RATIO, RELATIVE RISK, AND RISK DIFFERENCE FOR HARMS OUTCOMES

Cardiovascular death, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1% 50 mg/d	Placebo	3.54 (0.67, 23.88)	3.48 (0.67, 21.44)	0.02 (0.00, 0.11)
1% gel, 100 mg/d		1.66 (0.05, 46.10)	1.65 (0.05, 36.72)	0.00 (-0.01, 0.20)
1.62% gel, 40.5 mg/d		0.09 (0.00, 6.18)	0.09 (0.00, 6.00)	-0.01 (-0.01, 0.03)
2% gel, 60 mg/d		0.10 (0.00, 3.45)	0.10 (0.00, 3.40)	0.00 (-0.01, 0.01)
Oral TU 120 mg/d		0.24 (0.00, 18.95)	0.24 (0.00, 17.21)	0.00 (-0.01, 0.09)
Oral TU 120 or 160 mg/d		0.22 (0.00, 13.93)	0.22 (0.00, 13.01)	0.00 (-0.01, 0.07)
IM TU 1000 mg/12 wk		0.53 (0.08, 2.74)	0.54 (0.08, 2.72)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		0.15 (0.00, 5.82)	0.15 (0.00, 5.68)	0.00 (-0.01, 0.03)
IM TE 250 mg/3 wk		0.15 (0.00, 13.07)	0.15 (0.00, 12.12)	0.00 (-0.01, 0.07)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.48 (0.01, 18.20)	0.48 (0.01, 14.96)	-0.01 (-0.10, 0.18)
1.62% gel, 40.5 mg/d		0.02 (0.00, 2.11)	0.02 (0.00, 2.07)	-0.02 (-0.11, 0.01)
2% gel, 60 mg/d		0.03 (0.00, 1.57)	0.03 (0.00, 1.55)	-0.02 (-0.11, 0.01)
Oral TU 120 mg/d		0.06 (0.00, 6.72)	0.07 (0.00, 6.16)	-0.02 (-0.11, 0.07)
Oral TU 120 or 160 mg/d		0.06 (0.00, 5.48)	0.06 (0.00, 5.16)	-0.02 (-0.11, 0.05)
IM TU 1000 mg/12 wk		0.14 (0.01, 1.67)	0.15 (0.01, 1.66)	-0.02 (-0.11, 0.00)
IM TE 200 mg/2wk		0.04 (0.00, 2.30)	0.04 (0.00, 2.26)	-0.02 (-0.11, 0.01)
IM TE 250 mg/3 wk		0.04 (0.00, 4.60)	0.05 (0.00, 4.35)	-0.02 (-0.11, 0.05)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.05 (0.00, 12.34)	0.05 (0.00, 12.02)	-0.01 (-0.20, 0.02)
2% gel, 60 mg/d		0.06 (0.00, 10.53)	0.06 (0.00, 10.36)	-0.01 (-0.20, 0.01)
Oral TU 120 mg/d		0.14 (0.00, 43.77)	0.14 (0.00, 39.84)	-0.01 (-0.20, 0.08)
Oral TU 120 or 160 mg/d		0.13 (0.00, 27.64)	0.13 (0.00, 26.04)	-0.01 (-0.20, 0.06)
IM TU 1000 mg/12 wk		0.32 (0.01, 13.40)	0.32 (0.01, 13.28)	-0.01 (-0.20, 0.01)
IM TE 200 mg/2wk		0.08 (0.00, 13.95)	0.08 (0.00, 13.68)	-0.01 (-0.20, 0.02)
IM TE 250 mg/3 wk		0.09 (0.00, 24.03)	0.09 (0.00, 22.64)	-0.01 (-0.20, 0.06)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	1.12 (0.00, 401.30)	1.12 (0.00, 395.10)	0.00 (-0.03, 0.02)
Oral TU 120 mg/d		2.61 (0.00, 1684.00)	2.60 (0.00, 1548.00)	0.00 (-0.03, 0.10)
Oral TU 120 or 160 mg/d		2.56 (0.00, 1471.00)	2.55 (0.00, 1391.00)	0.00 (-0.03, 0.07)
IM TU 1000 mg/12 wk		6.03 (0.06, 985.20)	6.01 (0.06, 975.40)	0.00 (-0.03, 0.02)
IM TE 200 mg/2wk		1.65 (0.00, 760.10)	1.65 (0.00, 736.30)	0.00 (-0.03, 0.03)
IM TE 250 mg/3 wk		1.91 (0.00, 1186.00)	1.91 (0.00, 1134.00)	0.00 (-0.03, 0.07)
Oral TU 120 mg/d	2% gel, 60 mg/d	2.47 (0.00, 1683.00)	2.46 (0.00, 1566.00)	0.00 (-0.02, 0.10)
Oral TU 120 or 160 mg/d		2.43 (0.01, 1283.00)	2.42 (0.01, 1212.00)	0.00 (-0.02, 0.07)
IM TU 1000 mg/12 wk		5.33 (0.11, 979.60)	5.31 (0.11, 973.90)	0.00 (-0.02, 0.01)
IM TE 200 mg/2wk		1.49 (0.00, 781.70)	1.49 (0.00, 769.10)	0.00 (-0.02, 0.03)
IM TE 250 mg/3 wk		1.76 (0.00, 999.40)	1.76 (0.00, 945.60)	0.00 (-0.02, 0.07)
Oral TU 120 or 160 mg/d	Oral TU 120 mg/d	0.93 (0.00, 663.40)	0.93 (0.00, 643.30)	0.00 (-0.09, 0.07)
IM TU 1000 mg/12 wk		2.25 (0.02, 784.60)	2.24 (0.02, 780.20)	0.00 (-0.09, 0.01)
IM TE 200 mg/2wk		0.58 (0.00, 673.10)	0.58 (0.00, 659.80)	0.00 (-0.10, 0.03)
IM TE 250 mg/3 wk		0.72 (0.00, 718.60)	0.72 (0.00, 692.40)	0.00 (-0.09, 0.07)
IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	2.37 (0.03, 489.20)	2.37 (0.03, 485.70)	0.00 (-0.07, 0.01)

IM TE 200 mg/2wk		0.74 (0.00, 278.60)	0.74 (0.00, 272.40)	0.00 (-0.07, 0.03)
IM TE 250 mg/3 wk		0.77 (0.00, 596.10)	0.77 (0.00, 546.10)	0.00 (-0.07, 0.07)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.30 (0.00, 18.63)	0.30 (0.00, 18.19)	0.00 (-0.01, 0.03)
IM TE 250 mg/3 wk		0.30 (0.00, 23.49)	0.30 (0.00, 21.70)	0.00 (-0.01, 0.07)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	1.26 (0.00, 647.50)	1.26 (0.00, 615.80)	0.00 (-0.03, 0.07)

Cardiovascular death, adjusted continuity correction — odds ratios, relative risks, and risk difference for all treatment comparisons (random-effects model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1% 50 mg/d	Placebo	2.42 (0.63, 11.80)	2.37 (0.63, 10.47)	0.02 (-0.01, 0.12)
1% gel, 100 mg/d		1.52 (0.11, 22.14)	1.51 (0.11, 17.36)	0.01 (-0.02, 0.22)
1.62% gel, 40.5 mg/d		0.36 (0.01, 9.95)	0.36 (0.02, 8.98)	-0.01 (-0.02, 0.10)
2% gel, 60 mg/d		0.24 (0.01, 3.53)	0.24 (0.01, 3.42)	-0.01 (-0.02, 0.03)
Oral TU 120 mg/d		0.50 (0.01, 11.87)	0.51 (0.01, 10.36)	-0.01 (-0.02, 0.13)
Oral TU 120 or 160 mg/d		0.49 (0.01, 13.46)	0.49 (0.01, 11.62)	-0.01 (-0.02, 0.14)
IM TU 1000 mg/12 wk		0.66 (0.15, 2.59)	0.66 (0.15, 2.54)	0.00 (-0.02, 0.02)
IM TE 200 mg/2wk		0.53 (0.04, 6.33)	0.53 (0.04, 5.91)	-0.01 (-0.02, 0.06)
IM TE 250 mg/3 wk		0.41 (0.01, 13.71)	0.41 (0.01, 11.51)	-0.01 (-0.02, 0.16)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.61 (0.03, 13.11)	0.62 (0.03, 10.65)	-0.01 (-0.11, 0.20)
1.62% gel, 40.5 mg/d		0.14 (0.00, 5.29)	0.15 (0.00, 4.83)	-0.03 (-0.13, 0.08)
2% gel, 60 mg/d		0.09 (0.00, 2.04)	0.09 (0.00, 1.99)	-0.03 (-0.13, 0.02)
Oral TU 120 mg/d		0.20 (0.00, 5.83)	0.21 (0.00, 5.20)	-0.02 (-0.12, 0.10)
Oral TU 120 or 160 mg/d		0.19 (0.00, 7.52)	0.20 (0.00, 6.56)	-0.02 (-0.12, 0.13)
IM TU 1000 mg/12 wk		0.26 (0.03, 1.88)	0.27 (0.04, 1.85)	-0.02 (-0.12, 0.01)
IM TE 200 mg/2wk		0.21 (0.01, 3.85)	0.22 (0.01, 3.66)	-0.02 (-0.12, 0.05)
IM TE 250 mg/3 wk		0.16 (0.00, 7.15)	0.17 (0.00, 6.11)	-0.02 (-0.12, 0.14)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.23 (0.00, 14.45)	0.23 (0.00, 13.14)	-0.01 (-0.22, 0.09)
2% gel, 60 mg/d		0.14 (0.00, 6.92)	0.15 (0.00, 6.69)	-0.02 (-0.22, 0.03)
Oral TU 120 mg/d		0.32 (0.00, 18.43)	0.33 (0.00, 16.28)	-0.01 (-0.22, 0.11)
Oral TU 120 or 160 mg/d		0.30 (0.00, 24.13)	0.31 (0.00, 21.15)	-0.01 (-0.21, 0.13)
IM TU 1000 mg/12 wk		0.43 (0.02, 8.29)	0.44 (0.03, 8.15)	-0.01 (-0.22, 0.02)
IM TE 200 mg/2wk		0.34 (0.01, 13.52)	0.35 (0.01, 12.75)	-0.01 (-0.22, 0.06)
IM TE 250 mg/3 wk		0.27 (0.00, 18.98)	0.27 (0.00, 16.58)	-0.01 (-0.21, 0.14)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	0.60 (0.01, 44.76)	0.60 (0.01, 42.89)	0.00 (-0.11, 0.04)
Oral TU 120 mg/d		1.36 (0.01, 136.10)	1.35 (0.01, 124.40)	0.00 (-0.11, 0.13)
Oral TU 120 or 160 mg/d		1.32 (0.01, 140.70)	1.31 (0.01, 125.50)	0.00 (-0.11, 0.15)
IM TU 1000 mg/12 wk		1.86 (0.04, 52.83)	1.85 (0.05, 51.78)	0.00 (-0.11, 0.03)
IM TE 200 mg/2wk		1.43 (0.02, 74.77)	1.42 (0.03, 71.49)	0.00 (-0.11, 0.07)
IM TE 250 mg/3 wk		1.09 (0.01, 115.70)	1.09 (0.01, 102.50)	0.00 (-0.11, 0.16)
Oral TU 120 mg/d	2% gel, 60 mg/d	2.10 (0.02, 267.90)	2.08 (0.02, 242.80)	0.00 (-0.04, 0.13)
Oral TU 120 or 160 mg/d		2.16 (0.02, 214.70)	2.14 (0.02, 191.10)	0.00 (-0.04, 0.15)
IM TU 1000 mg/12 wk		2.82 (0.12, 115.90)	2.80 (0.12, 113.80)	0.01 (-0.04, 0.03)
IM TE 200 mg/2wk		2.29 (0.05, 149.80)	2.27 (0.05, 143.30)	0.00 (-0.04, 0.07)
IM TE 250 mg/3 wk		1.86 (0.01, 195.60)	1.85 (0.01, 168.30)	0.00 (-0.04, 0.16)
Oral TU 120 or 160 mg/d	Oral TU 120 mg/d	0.97 (0.01, 170.70)	0.97 (0.01, 150.80)	0.00 (-0.13, 0.15)
IM TU 1000 mg/12 wk		1.29 (0.04, 85.74)	1.29 (0.05, 84.37)	0.00 (-0.13, 0.03)
IM TE 200 mg/2wk		1.06 (0.02, 117.80)	1.06 (0.02, 112.40)	0.00 (-0.13, 0.07)
IM TE 250 mg/3 wk		0.85 (0.00, 157.40)	0.85 (0.00, 133.50)	0.00 (-0.13, 0.16)

IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	1.41 (0.03, 88.29)	1.41 (0.04, 87.10)	0.00 (-0.15, 0.03)
IM TE 200 mg/2wk		1.12 (0.01, 109.30)	1.12 (0.02, 104.30)	0.00 (-0.15, 0.07)
IM TE 250 mg/3 wk		0.86 (0.01, 143.80)	0.86 (0.01, 127.50)	0.00 (-0.14, 0.16)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.82 (0.04, 14.18)	0.82 (0.04, 13.17)	0.00 (-0.03, 0.07)
IM TE 250 mg/3 wk		0.64 (0.01, 18.85)	0.64 (0.01, 15.85)	0.00 (-0.02, 0.16)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	0.79 (0.01, 61.29)	0.79 (0.01, 51.49)	0.00 (-0.07, 0.16)

Cardiovascular death, continuity correction, treatments with zero events dropped — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1% 50 mg/d	Placebo	2.43 (0.59, 11.54)	2.38 (0.59, 10.52)	0.02 (-0.01, 0.09)
1% gel, 100 mg/d		1.49 (0.10, 21.29)	1.48 (0.10, 17.54)	0.01 (-0.02, 0.18)
IM TU 1000 mg/12 wk		0.62 (0.09, 3.42)	0.63 (0.09, 3.34)	0.00 (-0.02, 0.02)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.60 (0.03, 12.84)	0.61 (0.03, 10.64)	-0.01 (-0.09, 0.17)
IM TU 1000 mg/12 wk		0.25 (0.02, 2.31)	0.26 (0.02, 2.26)	-0.02 (-0.10, 0.02)
IM TU 1000 mg/12 wk	1% gel, 100 mg/d	0.42 (0.02, 10.50)	0.42 (0.02, 10.32)	-0.01 (-0.19, 0.02)

Myocardial infarction, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1%, 5 mg/d	Placebo	0.08 (0.00, 3.23)	0.09 (0.00, 3.14)	-0.01 (-0.02, 0.02)
Gel 1%, 50 mg/d		0.08 (0.00, 2.96)	0.08 (0.00, 2.90)	-0.01 (-0.02, 0.02)
Gel 1%, 100 mg/d		3.25 (0.20, 73.74)	3.16 (0.20, 42.31)	0.03 (-0.01, 0.43)
Gel 1.62%, 40.5 mg/d		0.56 (0.02, 18.65)	0.57 (0.02, 15.89)	0.00 (-0.02, 0.15)
Gel 2%, 60 mg/d		0.10 (0.00, 3.38)	0.10 (0.00, 3.30)	-0.01 (-0.02, 0.03)
Oral TU 160 mg/d		0.11 (0.00, 5.49)	0.11 (0.00, 5.23)	-0.01 (-0.02, 0.05)
IM TU, 1000 mg/12 wk		0.18 (0.02, 1.00)	0.18 (0.02, 1.00)	-0.01 (-0.02, 0.00)
IM TE, 200 mg/2wk		0.22 (0.00, 15.78)	0.22 (0.00, 13.65)	-0.01 (-0.02, 0.14)
Gel 1%, 50 mg/d	Gel 1%, 5 mg/d	1.01 (0.00, 408.50)	1.01 (0.00, 400.00)	0.00 (-0.03, 0.03)
Gel 1%, 100 mg/d		43.78 (0.39, 13850.00)	40.25 (0.40, 10130.00)	0.04 (-0.01, 0.44)
Gel 1.62%, 40.5 mg/d		7.46 (0.05, 2541.00)	7.36 (0.05, 2218.00)	0.00 (-0.03, 0.15)
Gel 2%, 60 mg/d		1.12 (0.00, 376.00)	1.12 (0.00, 364.20)	0.00 (-0.03, 0.03)
Oral TU 160 mg/d		1.38 (0.00, 498.00)	1.38 (0.00, 483.80)	0.00 (-0.03, 0.06)
IM TU, 1000 mg/12 wk		2.18 (0.03, 380.00)	2.18 (0.03, 376.80)	0.00 (-0.03, 0.01)
IM TE, 200 mg/2wk		2.82 (0.01, 1437.00)	2.80 (0.01, 1272.00)	0.00 (-0.03, 0.14)
Gel 1%, 100 mg/d	Gel 1%, 50 mg/d	41.26 (0.39, 12040.00)	37.93 (0.40, 8885.00)	0.04 (-0.01, 0.44)
Gel 1.62%, 40.5 mg/d		6.95 (0.05, 2349.00)	6.86 (0.05, 2127.00)	0.00 (-0.02, 0.15)
Gel 2%, 60 mg/d		1.15 (0.00, 380.90)	1.14 (0.00, 367.70)	0.00 (-0.03, 0.03)
Oral TU 160 mg/d		1.40 (0.00, 540.70)	1.40 (0.00, 517.90)	0.00 (-0.03, 0.06)
IM TU, 1000 mg/12 wk		2.15 (0.03, 348.20)	2.15 (0.03, 346.50)	0.00 (-0.03, 0.01)
IM TE, 200 mg/2wk		2.68 (0.00, 1694.00)	2.67 (0.00, 1512.00)	0.00 (-0.03, 0.14)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.16 (0.00, 14.67)	0.17 (0.00, 12.95)	-0.03 (-0.43, 0.12)
Gel 2%, 60 mg/d		0.03 (0.00, 2.80)	0.03 (0.00, 2.75)	-0.04 (-0.44, 0.01)
Oral TU 160 mg/d		0.03 (0.00, 4.73)	0.03 (0.00, 4.52)	-0.03 (-0.44, 0.03)
IM TU, 1000 mg/12 wk		0.05 (0.00, 1.43)	0.06 (0.00, 1.43)	-0.04 (-0.44, 0.00)
IM TE, 200 mg/2wk		0.06 (0.00, 12.33)	0.07 (0.00, 11.02)	-0.03 (-0.43, 0.10)

Gel 2%, 60 mg/d	Gel 1.62%, 40.5 mg/d	0.17 (0.00, 21.67)	0.17 (0.00, 20.95)	0.00 (-0.15, 0.03)
Oral TU 160 mg/d		0.19 (0.00, 33.68)	0.19 (0.00, 32.15)	0.00 (-0.15, 0.05)
IM TU, 1000 mg/12 wk		0.31 (0.01, 12.85)	0.31 (0.01, 12.81)	0.00 (-0.15, 0.01)
IM TE, 200 mg/2wk		0.38 (0.00, 81.30)	0.39 (0.00, 71.26)	0.00 (-0.15, 0.13)
Oral TU 160 mg/d	Gel 2%, 60 mg/d	1.18 (0.00, 701.70)	1.17 (0.00, 666.90)	0.00 (-0.03, 0.06)
IM TU, 1000 mg/12 wk		1.88 (0.03, 494.50)	1.87 (0.03, 492.30)	0.00 (-0.04, 0.01)
IM TE, 200 mg/2wk		2.34 (0.00, 1989.00)	2.33 (0.00, 1795.00)	0.00 (-0.03, 0.14)
IM TU, 1000 mg/12 wk	Oral TU 160 mg/d	1.52 (0.02, 289.00)	1.52 (0.02, 287.60)	0.00 (-0.06, 0.01)
IM TE, 200 mg/2wk		2.11 (0.00, 1422.00)	2.10 (0.00, 1277.00)	0.00 (-0.05, 0.14)
IM TE, 200 mg/2wk	IM TU, 1000 mg/12 wk	1.26 (0.00, 150.60)	1.26 (0.00, 126.30)	0.00 (-0.01, 0.14)

Myocardial infarction, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1%, 5 mg/d	Placebo	0.26 (0.01, 4.18)	0.27 (0.01, 3.93)	-0.01 (-0.03, 0.06)
Gel 1%, 50 mg/d		0.25 (0.01, 4.13)	0.25 (0.01, 3.90)	-0.01 (-0.03, 0.06)
Gel 1%, 100 mg/d		2.45 (0.23, 38.53)	2.38 (0.24, 23.40)	0.03 (-0.02, 0.40)
Gel 1.62%, 40.5 mg/d		0.73 (0.05, 15.62)	0.73 (0.05, 12.46)	-0.01 (-0.03, 0.20)
Gel 2%, 60 mg/d		0.26 (0.01, 3.72)	0.26 (0.01, 3.54)	-0.01 (-0.03, 0.05)
Oral TU 160 mg/d		0.50 (0.01, 8.96)	0.51 (0.01, 7.84)	-0.01 (-0.03, 0.13)
IM TU, 1000 mg/12 wk		0.27 (0.05, 1.03)	0.27 (0.05, 1.03)	-0.01 (-0.03, 0.00)
IM TE, 200 mg/2wk		0.54 (0.01, 14.15)	0.55 (0.01, 11.47)	-0.01 (-0.03, 0.19)
Gel 1%, 50 mg/d	Gel 1%, 5 mg/d	0.98 (0.01, 68.23)	0.98 (0.01, 65.19)	0.00 (-0.07, 0.07)
Gel 1%, 100 mg/d		10.11 (0.24, 785.80)	9.44 (0.25, 548.10)	0.04 (-0.04, 0.41)
Gel 1.62%, 40.5 mg/d		3.04 (0.06, 239.00)	2.98 (0.06, 205.90)	0.01 (-0.06, 0.20)
Gel 2%, 60 mg/d		1.01 (0.01, 74.16)	1.01 (0.01, 70.74)	0.00 (-0.07, 0.06)
Oral TU 160 mg/d		1.86 (0.02, 175.70)	1.85 (0.02, 159.90)	0.00 (-0.06, 0.14)
IM TU, 1000 mg/12 wk		1.01 (0.04, 44.17)	1.01 (0.04, 43.74)	0.00 (-0.07, 0.02)
IM TE, 200 mg/2wk		2.10 (0.02, 257.40)	2.08 (0.02, 219.00)	0.00 (-0.06, 0.20)
Gel 1%, 100 mg/d	Gel 1%, 50 mg/d	10.90 (0.25, 1078.00)	10.12 (0.26, 792.30)	0.04 (-0.04, 0.40)
Gel 1.62%, 40.5 mg/d		3.24 (0.05, 327.40)	3.18 (0.06, 279.50)	0.01 (-0.06, 0.21)
Gel 2%, 60 mg/d		1.07 (0.01, 99.67)	1.07 (0.01, 94.63)	0.00 (-0.07, 0.06)
Oral TU 160 mg/d		2.07 (0.02, 205.90)	2.05 (0.02, 187.70)	0.00 (-0.06, 0.14)
IM TU, 1000 mg/12 wk		1.06 (0.04, 56.73)	1.06 (0.04, 56.22)	0.00 (-0.07, 0.02)
IM TE, 200 mg/2wk		2.17 (0.02, 286.80)	2.15 (0.02, 242.80)	0.00 (-0.06, 0.20)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.29 (0.01, 14.45)	0.30 (0.01, 11.89)	-0.03 (-0.39, 0.17)
Gel 2%, 60 mg/d		0.10 (0.00, 3.75)	0.10 (0.00, 3.57)	-0.04 (-0.41, 0.03)
Oral TU 160 mg/d		0.19 (0.00, 8.32)	0.20 (0.00, 7.56)	-0.03 (-0.40, 0.10)
IM TU, 1000 mg/12 wk		0.10 (0.00, 1.74)	0.11 (0.01, 1.73)	-0.04 (-0.41, 0.00)
IM TE, 200 mg/2wk		0.20 (0.00, 11.82)	0.21 (0.00, 10.02)	-0.03 (-0.39, 0.15)
Gel 2%, 60 mg/d	Gel 1.62%, 40.5 mg/d	0.33 (0.00, 17.20)	0.33 (0.00, 16.32)	-0.01 (-0.21, 0.05)
Oral TU 160 mg/d		0.66 (0.01, 34.63)	0.67 (0.01, 31.12)	0.00 (-0.20, 0.13)
IM TU, 1000 mg/12 wk		0.35 (0.01, 7.30)	0.36 (0.01, 7.21)	-0.01 (-0.21, 0.01)
IM TE, 200 mg/2wk		0.70 (0.00, 48.97)	0.71 (0.01, 41.14)	0.00 (-0.20, 0.19)
Oral TU 160 mg/d	Gel 2%, 60 mg/d	1.98 (0.02, 205.10)	1.96 (0.03, 187.40)	0.00 (-0.06, 0.13)
IM TU, 1000 mg/12 wk		1.04 (0.04, 51.62)	1.04 (0.05, 51.08)	0.00 (-0.07, 0.01)
IM TE, 200 mg/2wk		2.14 (0.02, 260.50)	2.11 (0.02, 220.60)	0.00 (-0.06, 0.20)

IM TU, 1000 mg/12 wk	Oral TU 160 mg/d	0.52 (0.03, 20.35)	0.52 (0.03, 20.19)	0.00 (-0.14, 0.01)
IM TE, 200 mg/2wk		1.07 (0.01, 114.80)	1.07 (0.01, 98.94)	0.00 (-0.13, 0.19)
IM TE, 200 mg/2wk	IM TU, 1000 mg/12 wk	2.01 (0.03, 73.92)	2.00 (0.03, 58.98)	0.01 (-0.01, 0.21)

Myocardial infarction, continuity correction, treatments with zero events dropped — Odds Ratios, Relative Risks and Risk Difference (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1%, 100 mg/d	Placebo	2.56 (0.25, 35.03)	2.48 (0.25, 23.83)	0.03 (-0.02, 0.32)
Gel 1.62%, 40.5 mg/d		0.72 (0.05, 16.19)	0.72 (0.05, 13.76)	0.00 (-0.03, 0.16)
IM TU, 1000 mg/12 wk		0.43 (0.08, 2.08)	0.44 (0.08, 2.05)	-0.01 (-0.03, 0.01)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.28 (0.01, 13.92)	0.29 (0.01, 12.01)	-0.03 (-0.32, 0.13)
IM TU, 1000 mg/12 wk		0.17 (0.01, 2.72)	0.18 (0.01, 2.69)	-0.04 (-0.33, 0.01)
IM TU, 1000 mg/12 wk	Gel 1.62%, 40.5 mg/d	0.58 (0.02, 13.51)	0.58 (0.02, 13.22)	-0.01 (-0.17, 0.02)

Prostate cancer, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	7.36 (0.66, 129.00)	7.28 (0.66, 114.80)	0.00 (0.00, 0.13)
Gel 5 mg/d		0.96 (0.04, 22.24)	0.96 (0.04, 21.52)	0.00 (0.00, 0.03)
Gel 1% 50 mg/d		0.66 (0.04, 8.90)	0.66 (0.04, 8.82)	0.00 (0.00, 0.01)
Gel 1% 100 mg/d		1.41 (0.06, 32.28)	1.41 (0.06, 31.37)	0.00 (0.00, 0.03)
Oral TU 160 mg/d		0.08 (0.00, 2.11)	0.08 (0.00, 2.11)	0.00 (-0.01, 0.00)
IM TU 1000 mg/12 wk		0.14 (0.00, 6.83)	0.14 (0.00, 6.79)	0.00 (-0.01, 0.01)
IM TE 150 mg/2wk		0.45 (0.05, 3.76)	0.45 (0.05, 3.75)	0.00 (0.00, 0.00)
IM TE 200 mg/2wk		5.99 (0.65, 91.39)	5.95 (0.65, 83.68)	0.00 (0.00, 0.11)
IM TE 250 mg/4wk		0.99 (0.00, 438.50)	0.99 (0.00, 296.70)	0.00 (-0.01, 0.27)
Gel 5 mg/d	Patch 5 mg/d	0.12 (0.00, 6.93)	0.13 (0.00, 6.77)	0.00 (-0.13, 0.02)
Gel 1% 50 mg/d		0.09 (0.00, 2.21)	0.09 (0.00, 2.20)	0.00 (-0.13, 0.00)
Gel 1% 100 mg/d		0.20 (0.00, 4.60)	0.20 (0.00, 4.53)	0.00 (-0.12, 0.01)
Oral TU 160 mg/d		0.01 (0.00, 0.67)	0.01 (0.00, 0.67)	-0.01 (-0.14, 0.00)
IM TU 1000 mg/12 wk		0.02 (0.00, 1.93)	0.02 (0.00, 1.93)	0.00 (-0.13, 0.00)
IM TE 150 mg/2wk		0.06 (0.00, 1.53)	0.06 (0.00, 1.52)	0.00 (-0.13, 0.00)
IM TE 200 mg/2wk		0.84 (0.07, 9.18)	0.85 (0.07, 8.81)	0.00 (-0.09, 0.06)
IM TE 250 mg/4wk		0.12 (0.00, 94.67)	0.12 (0.00, 69.32)	0.00 (-0.13, 0.25)
Gel 1% 50 mg/d	Gel 5 mg/d	0.70 (0.01, 37.31)	0.71 (0.01, 36.92)	0.00 (-0.03, 0.01)
Gel 1% 100 mg/d		1.54 (0.02, 119.30)	1.53 (0.02, 117.00)	0.00 (-0.03, 0.03)
Oral TU 160 mg/d		0.07 (0.00, 7.20)	0.07 (0.00, 7.19)	0.00 (-0.03, 0.00)
IM TU 1000 mg/12 wk		0.14 (0.00, 21.32)	0.14 (0.00, 21.12)	0.00 (-0.03, 0.01)
IM TE 150 mg/2wk		0.46 (0.01, 22.35)	0.46 (0.01, 22.24)	0.00 (-0.03, 0.00)
IM TE 200 mg/2wk		6.74 (0.12, 347.60)	6.67 (0.12, 329.20)	0.00 (-0.02, 0.11)
IM TE 250 mg/4wk		0.98 (0.00, 1017.00)	0.98 (0.00, 748.40)	0.00 (-0.03, 0.27)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	2.17 (0.05, 110.80)	2.17 (0.05, 108.50)	0.00 (-0.01, 0.03)
Oral TU 160 mg/d		0.11 (0.00, 9.33)	0.11 (0.00, 9.32)	0.00 (-0.01, 0.00)
IM TU 1000 mg/12 wk		0.21 (0.00, 25.28)	0.21 (0.00, 25.02)	0.00 (-0.01, 0.01)
IM TE 150 mg/2wk		0.67 (0.02, 22.70)	0.67 (0.02, 22.63)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		9.28 (0.35, 414.10)	9.16 (0.35, 388.20)	0.00 (0.00, 0.11)

IM TE 250 mg/4wk		1.51 (0.00, 1268.00)	1.51 (0.00, 920.90)	0.00 (-0.01, 0.27)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.05 (0.00, 5.41)	0.05 (0.00, 5.40)	0.00 (-0.04, 0.00)
IM TU 1000 mg/12 wk		0.09 (0.00, 15.41)	0.09 (0.00, 15.32)	0.00 (-0.04, 0.01)
IM TE 150 mg/2wk		0.31 (0.01, 13.41)	0.31 (0.01, 13.37)	0.00 (-0.04, 0.00)
IM TE 200 mg/2wk		4.29 (0.14, 198.70)	4.24 (0.15, 190.30)	0.00 (-0.02, 0.11)
IM TE 250 mg/4wk		0.67 (0.00, 623.00)	0.67 (0.00, 466.70)	0.00 (-0.03, 0.27)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.96 (0.00, 726.20)	1.96 (0.00, 721.70)	0.00 (0.00, 0.01)
IM TE 150 mg/2wk		6.03 (0.11, 971.10)	6.02 (0.11, 970.20)	0.00 (0.00, 0.01)
IM TE 200 mg/2wk		89.45 (1.36, 19420.00)	88.08 (1.36, 18380.00)	0.00 (0.00, 0.11)
IM TE 250 mg/4wk		12.97 (0.01, 32540.00)	12.91 (0.01, 25250.00)	0.00 (0.00, 0.27)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	3.33 (0.04, 741.00)	3.33 (0.04, 738.60)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		47.38 (0.46, 11490.00)	46.58 (0.47, 11130.00)	0.00 (0.00, 0.11)
IM TE 250 mg/4wk		7.98 (0.00, 13500.00)	7.93 (0.00, 10740.00)	0.00 (-0.01, 0.27)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	13.84 (0.59, 429.50)	13.67 (0.59, 400.70)	0.00 (0.00, 0.11)
IM TE 250 mg/4wk		2.20 (0.00, 1325.00)	2.19 (0.00, 945.90)	0.00 (-0.01, 0.27)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.15 (0.00, 105.70)	0.16 (0.00, 72.15)	0.00 (-0.10, 0.25)

Prostate cancer, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	2.63 (0.38, 20.55)	2.56 (0.39, 16.17)	0.03 (-0.01, 0.21)
Gel 5 mg/d		0.61 (0.03, 9.09)	0.61 (0.03, 8.12)	-0.01 (-0.02, 0.10)
Gel 1% 50 mg/d		0.56 (0.09, 2.87)	0.57 (0.09, 2.80)	-0.01 (-0.02, 0.02)
Gel 1% 100 mg/d		0.81 (0.09, 6.07)	0.81 (0.09, 5.69)	0.00 (-0.02, 0.07)
Oral TU 160 mg/d		0.17 (0.01, 2.18)	0.18 (0.01, 2.14)	-0.01 (-0.02, 0.02)
IM TU 1000 mg/12 wk		0.27 (0.01, 4.12)	0.27 (0.01, 3.93)	-0.01 (-0.02, 0.05)
IM TE 150 mg/2wk		0.44 (0.05, 3.15)	0.44 (0.05, 3.05)	-0.01 (-0.02, 0.03)
IM TE 200 mg/2wk		2.54 (0.37, 18.99)	2.48 (0.38, 15.19)	0.02 (-0.01, 0.20)
IM TE 250 mg/4wk		0.53 (0.01, 13.77)	0.53 (0.01, 11.66)	-0.01 (-0.02, 0.15)
Gel 5 mg/d	Patch 5 mg/d	0.23 (0.01, 6.19)	0.24 (0.01, 5.62)	-0.03 (-0.22, 0.08)
Gel 1% 50 mg/d		0.21 (0.02, 2.14)	0.22 (0.02, 2.11)	-0.03 (-0.22, 0.01)
Gel 1% 100 mg/d		0.31 (0.02, 3.21)	0.32 (0.02, 3.08)	-0.03 (-0.21, 0.04)
Oral TU 160 mg/d		0.06 (0.00, 1.74)	0.07 (0.00, 1.72)	-0.04 (-0.22, 0.01)
IM TU 1000 mg/12 wk		0.10 (0.00, 2.94)	0.10 (0.00, 2.83)	-0.03 (-0.22, 0.03)
IM TE 150 mg/2wk		0.16 (0.01, 2.66)	0.17 (0.01, 2.59)	-0.03 (-0.22, 0.02)
IM TE 200 mg/2wk		0.96 (0.13, 7.14)	0.96 (0.14, 6.37)	0.00 (-0.15, 0.14)
IM TE 250 mg/4wk		0.19 (0.00, 7.63)	0.20 (0.00, 6.68)	-0.03 (-0.22, 0.12)
Gel 1% 50 mg/d	Gel 5 mg/d	0.93 (0.04, 23.22)	0.94 (0.04, 22.81)	0.00 (-0.11, 0.03)
Gel 1% 100 mg/d		1.35 (0.04, 49.21)	1.35 (0.04, 46.46)	0.00 (-0.11, 0.07)
Oral TU 160 mg/d		0.28 (0.00, 12.88)	0.28 (0.00, 12.53)	-0.01 (-0.11, 0.02)
IM TU 1000 mg/12 wk		0.43 (0.00, 21.55)	0.43 (0.01, 20.64)	0.00 (-0.11, 0.05)
IM TE 150 mg/2wk		0.72 (0.03, 26.81)	0.72 (0.03, 26.04)	0.00 (-0.11, 0.04)
IM TE 200 mg/2wk		4.27 (0.15, 144.50)	4.09 (0.17, 124.50)	0.03 (-0.08, 0.20)
IM TE 250 mg/4wk		0.83 (0.01, 61.46)	0.83 (0.01, 54.42)	0.00 (-0.11, 0.15)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.45 (0.10, 20.24)	1.44 (0.11, 19.09)	0.00 (-0.03, 0.07)
Oral TU 160 mg/d		0.31 (0.01, 6.23)	0.31 (0.01, 6.07)	-0.01 (-0.04, 0.03)
IM TU 1000 mg/12 wk		0.48 (0.01, 13.15)	0.48 (0.01, 12.30)	0.00 (-0.04, 0.05)
IM TE 150 mg/2wk		0.78 (0.05, 12.46)	0.78 (0.06, 12.00)	0.00 (-0.03, 0.04)

IM TE 200 mg/2wk		4.59 (0.42, 61.23)	4.41 (0.43, 51.01)	0.03 (-0.02, 0.21)
IM TE 250 mg/4wk		0.92 (0.02, 38.30)	0.93 (0.02, 32.68)	0.00 (-0.03, 0.15)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.20 (0.00, 6.92)	0.20 (0.00, 6.79)	-0.01 (-0.08, 0.02)
IM TU 1000 mg/12 wk		0.32 (0.00, 10.33)	0.32 (0.00, 9.83)	-0.01 (-0.07, 0.05)
IM TE 150 mg/2wk		0.53 (0.03, 9.84)	0.54 (0.03, 9.49)	-0.01 (-0.07, 0.04)
IM TE 200 mg/2wk		3.13 (0.23, 53.26)	3.01 (0.24, 46.02)	0.02 (-0.04, 0.20)
IM TE 250 mg/4wk		0.64 (0.01, 31.74)	0.65 (0.01, 27.23)	0.00 (-0.07, 0.15)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.54 (0.02, 121.90)	1.53 (0.02, 116.40)	0.00 (-0.03, 0.06)
IM TE 150 mg/2wk		2.63 (0.09, 132.80)	2.61 (0.10, 129.00)	0.00 (-0.03, 0.05)
IM TE 200 mg/2wk		15.33 (0.57, 932.00)	14.52 (0.57, 813.40)	0.04 (-0.01, 0.21)
IM TE 250 mg/4wk		3.14 (0.03, 353.00)	3.11 (0.04, 309.40)	0.00 (-0.03, 0.16)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	1.68 (0.05, 103.80)	1.67 (0.06, 100.20)	0.00 (-0.05, 0.04)
IM TE 200 mg/2wk		9.85 (0.33, 722.30)	9.36 (0.34, 639.50)	0.03 (-0.03, 0.21)
IM TE 250 mg/4wk		1.99 (0.02, 244.70)	1.98 (0.02, 215.50)	0.00 (-0.05, 0.16)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	5.92 (0.37, 99.96)	5.68 (0.38, 83.37)	0.03 (-0.02, 0.21)
IM TE 250 mg/4wk		1.16 (0.02, 57.94)	1.16 (0.02, 49.87)	0.00 (-0.04, 0.15)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.20 (0.00, 8.57)	0.21 (0.00, 7.42)	-0.03 (-0.20, 0.13)

Prostate cancer, continuity correction, treatments with zero events dropped — Odds Ratios, Relative Risks and Risk Difference (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	2.88 (0.42, 20.23)	2.86 (0.42, 19.44)	0.01 (0.00, 0.05)
Gel 5 mg/d		0.64 (0.03, 9.38)	0.65 (0.03, 9.14)	0.00 (-0.01, 0.02)
Gel 1% 50 mg/d		0.58 (0.08, 2.85)	0.58 (0.08, 2.83)	0.00 (-0.01, 0.00)
Gel 1% 100 mg/d		0.82 (0.08, 5.36)	0.82 (0.09, 5.31)	0.00 (-0.01, 0.01)
IM TE 150 mg/2wk		0.43 (0.05, 2.97)	0.43 (0.05, 2.95)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		2.73 (0.38, 21.45)	2.71 (0.38, 20.44)	0.01 (0.00, 0.05)
Gel 5 mg/d	Patch 5 mg/d	0.22 (0.01, 6.53)	0.22 (0.01, 6.41)	-0.01 (-0.05, 0.02)
Gel 1% 50 mg/d		0.20 (0.01, 2.13)	0.20 (0.02, 2.12)	-0.01 (-0.05, 0.00)
Gel 1% 100 mg/d		0.29 (0.02, 3.04)	0.29 (0.02, 3.01)	-0.01 (-0.05, 0.01)
IM TE 150 mg/2wk		0.15 (0.01, 2.30)	0.15 (0.01, 2.29)	-0.01 (-0.05, 0.00)
IM TE 200 mg/2wk		0.94 (0.12, 7.25)	0.94 (0.12, 7.09)	0.00 (-0.03, 0.03)
Gel 1% 50 mg/d	Gel 5 mg/d	0.91 (0.03, 25.01)	0.91 (0.03, 24.87)	0.00 (-0.02, 0.01)
Gel 1% 100 mg/d		1.27 (0.04, 38.86)	1.26 (0.04, 38.58)	0.00 (-0.02, 0.01)
IM TE 150 mg/2wk		0.67 (0.02, 22.28)	0.67 (0.02, 22.17)	0.00 (-0.02, 0.01)
IM TE 200 mg/2wk		4.26 (0.15, 164.00)	4.22 (0.15, 158.60)	0.01 (-0.02, 0.05)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.43 (0.10, 19.81)	1.43 (0.10, 19.61)	0.00 (-0.01, 0.01)
IM TE 150 mg/2wk		0.76 (0.05, 10.93)	0.76 (0.05, 10.87)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		4.89 (0.37, 71.65)	4.85 (0.37, 68.88)	0.01 (0.00, 0.05)
IM TE 150 mg/2wk	Gel 1% 100 mg/d	0.52 (0.03, 10.11)	0.52 (0.03, 10.06)	0.00 (-0.01, 0.01)
IM TE 200 mg/2wk		3.34 (0.25, 60.92)	3.32 (0.25, 58.70)	0.01 (-0.01, 0.05)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	6.25 (0.41, 125.90)	6.19 (0.41, 121.00)	0.01 (0.00, 0.05)

Serious adverse events, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	1.14 (0.06, 15.71)	1.14 (0.06, 10.86)	0.00 (-0.04, 0.30)
Gel 1% 50 mg/d		1.35 (0.48, 3.86)	1.33 (0.49, 3.53)	0.01 (-0.02, 0.09)
Gel 1% 100 mg/d		1.35 (0.47, 3.41)	1.33 (0.48, 3.16)	0.01 (-0.02, 0.08)
Gel 1% 125 mg/d		2.57 (0.10, 98.48)	2.43 (0.10, 26.62)	0.05 (-0.04, 0.71)
Gel 1.62% 40.5 mg/d		0.74 (0.11, 7.32)	0.75 (0.12, 6.13)	-0.01 (-0.04, 0.16)
Oral TU 160 mg/d		0.43 (0.10, 1.62)	0.44 (0.11, 1.59)	-0.02 (-0.04, 0.02)
IM TU 1000 mg/9 wk		6.31 (0.06, 1541.00)	5.29 (0.06, 33.48)	0.15 (-0.04, 0.95)
IM TU 1000 mg/12 wk		0.29 (0.06, 1.16)	0.30 (0.06, 1.15)	-0.02 (-0.05, 0.00)
IM TE 250 mg/3 wk		1.49 (0.06, 24.34)	1.46 (0.06, 14.17)	0.02 (-0.04, 0.41)
Gel 1% 50 mg/d	Patch 5 mg/d	1.18 (0.07, 26.32)	1.17 (0.10, 24.42)	0.01 (-0.29, 0.10)
Gel 1% 100 mg/d		1.18 (0.07, 24.46)	1.17 (0.10, 22.87)	0.01 (-0.29, 0.09)
Gel 1% 125 mg/d		2.51 (0.04, 200.90)	2.28 (0.05, 82.19)	0.04 (-0.25, 0.69)
Gel 1.62% 40.5 mg/d		0.66 (0.03, 24.88)	0.68 (0.04, 21.91)	-0.01 (-0.30, 0.15)
Oral TU 160 mg/d		0.38 (0.02, 9.17)	0.39 (0.03, 8.89)	-0.02 (-0.32, 0.03)
IM TU 1000 mg/9 wk		5.33 (0.05, 1846.00)	3.89 (0.06, 126.90)	0.12 (-0.16, 0.93)
IM TU 1000 mg/12 wk		0.25 (0.01, 7.01)	0.26 (0.02, 6.85)	-0.03 (-0.32, 0.02)
IM TE 250 mg/3 wk		1.36 (0.23, 6.12)	1.32 (0.25, 5.23)	0.01 (-0.10, 0.22)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.00 (0.22, 3.95)	1.00 (0.24, 3.69)	0.00 (-0.08, 0.07)
Gel 1% 125 mg/d		1.90 (0.06, 80.61)	1.82 (0.07, 24.42)	0.04 (-0.09, 0.70)
Gel 1.62% 40.5 mg/d		0.56 (0.06, 6.53)	0.58 (0.07, 5.61)	-0.02 (-0.10, 0.15)
Oral TU 160 mg/d		0.32 (0.05, 1.74)	0.33 (0.06, 1.70)	-0.03 (-0.11, 0.02)
IM TU 1000 mg/9 wk		4.69 (0.04, 1207.00)	3.90 (0.04, 35.67)	0.13 (-0.08, 0.93)
IM TU 1000 mg/12 wk		0.21 (0.03, 1.23)	0.22 (0.03, 1.22)	-0.03 (-0.11, 0.01)
IM TE 250 mg/3 wk		1.09 (0.04, 21.89)	1.09 (0.04, 13.20)	0.00 (-0.09, 0.40)
Gel 1% 125 mg/d	Gel 1% 100 mg/d	1.93 (0.07, 84.36)	1.84 (0.07, 24.73)	0.04 (-0.08, 0.70)
Gel 1.62% 40.5 mg/d		0.56 (0.07, 6.86)	0.58 (0.07, 5.79)	-0.02 (-0.09, 0.15)
Oral TU 160 mg/d		0.32 (0.06, 1.74)	0.33 (0.07, 1.71)	-0.03 (-0.10, 0.02)
IM TU 1000 mg/9 wk		4.76 (0.04, 1221.00)	3.99 (0.04, 35.68)	0.13 (-0.07, 0.93)
IM TU 1000 mg/12 wk		0.21 (0.03, 1.24)	0.22 (0.04, 1.24)	-0.03 (-0.10, 0.01)
IM TE 250 mg/3 wk		1.10 (0.04, 22.14)	1.09 (0.05, 13.44)	0.00 (-0.08, 0.40)
Gel 1.62% 40.5 mg/d	Gel 1% 125 mg/d	0.30 (0.00, 16.80)	0.32 (0.01, 14.58)	-0.05 (-0.71, 0.13)
Oral TU 160 mg/d		0.17 (0.00, 5.59)	0.18 (0.01, 5.42)	-0.07 (-0.73, 0.03)
IM TU 1000 mg/9 wk		2.44 (0.01, 1316.00)	1.91 (0.02, 97.27)	0.07 (-0.59, 0.92)
IM TU 1000 mg/12 wk		0.11 (0.00, 3.52)	0.12 (0.01, 3.47)	-0.07 (-0.73, 0.01)
IM TE 250 mg/3 wk		0.52 (0.00, 38.90)	0.56 (0.01, 28.07)	-0.03 (-0.67, 0.35)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.57 (0.04, 5.62)	0.58 (0.05, 5.41)	-0.01 (-0.18, 0.04)
IM TU 1000 mg/9 wk		8.02 (0.04, 2338.00)	6.10 (0.05, 109.50)	0.14 (-0.10, 0.95)
IM TU 1000 mg/12 wk		0.38 (0.02, 4.08)	0.38 (0.03, 3.99)	-0.01 (-0.18, 0.02)
IM TE 250 mg/3 wk		1.92 (0.04, 54.23)	1.86 (0.05, 35.72)	0.02 (-0.14, 0.41)
IM TU 1000 mg/9 wk	Oral TU 160 mg/d	15.33 (0.12, 4135.00)	11.93 (0.12, 135.30)	0.17 (-0.02, 0.96)
IM TU 1000 mg/12 wk		0.67 (0.09, 4.84)	0.67 (0.09, 4.72)	0.00 (-0.05, 0.03)
IM TE 250 mg/3 wk		3.48 (0.11, 79.25)	3.32 (0.12, 48.84)	0.03 (-0.03, 0.43)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.04 (0.00, 6.42)	0.06 (0.00, 6.32)	-0.17 (-0.97, 0.02)
IM TE 250 mg/3 wk		0.24 (0.00, 23.82)	0.33 (0.01, 20.02)	-0.10 (-0.92, 0.24)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	5.37 (0.16, 128.60)	5.08 (0.16, 78.77)	0.04 (-0.02, 0.43)

Serious adverse events, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	1.17 (0.11, 16.03)	1.16 (0.12, 10.07)	0.01 (-0.05, 0.36)
Gel 1% 50 mg/d		1.34 (0.49, 3.73)	1.32 (0.50, 3.35)	0.01 (-0.02, 0.10)
Gel 1% 100 mg/d		1.35 (0.48, 3.47)	1.33 (0.50, 3.14)	0.01 (-0.02, 0.09)
Gel 1% 125 mg/d		2.13 (0.12, 45.14)	2.03 (0.13, 16.78)	0.05 (-0.05, 0.61)
Gel 1.62% 40.5 mg/d		0.73 (0.11, 7.62)	0.74 (0.12, 6.05)	-0.01 (-0.05, 0.20)
Oral TU 160 mg/d		0.45 (0.11, 1.55)	0.46 (0.12, 1.52)	-0.02 (-0.05, 0.02)
IM TU 1000 mg/9 wk		2.90 (0.06, 201.30)	2.67 (0.07, 21.63)	0.07 (-0.05, 0.86)
IM TU 1000 mg/12 wk		0.34 (0.08, 1.22)	0.35 (0.08, 1.21)	-0.03 (-0.05, 0.01)
IM TE 250 mg/3 wk		1.65 (0.11, 27.15)	1.60 (0.11, 13.35)	0.03 (-0.05, 0.49)
Gel 1% 50 mg/d	Patch 5 mg/d	1.14 (0.07, 14.84)	1.14 (0.11, 13.46)	0.01 (-0.35, 0.11)
Gel 1% 100 mg/d		1.14 (0.07, 14.58)	1.13 (0.11, 13.27)	0.01 (-0.35, 0.11)
Gel 1% 125 mg/d		1.77 (0.04, 87.70)	1.67 (0.06, 42.36)	0.03 (-0.32, 0.60)
Gel 1.62% 40.5 mg/d		0.63 (0.03, 17.52)	0.64 (0.04, 14.58)	-0.01 (-0.36, 0.19)
Oral TU 160 mg/d		0.38 (0.02, 5.50)	0.39 (0.03, 5.28)	-0.03 (-0.38, 0.04)
IM TU 1000 mg/9 wk		2.32 (0.06, 162.40)	2.03 (0.07, 34.41)	0.05 (-0.20, 0.80)
IM TU 1000 mg/12 wk		0.28 (0.02, 4.24)	0.29 (0.02, 4.13)	-0.04 (-0.39, 0.02)
IM TE 250 mg/3 wk		1.44 (0.25, 6.18)	1.37 (0.28, 5.02)	0.01 (-0.10, 0.27)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.00 (0.23, 3.96)	1.00 (0.26, 3.63)	0.00 (-0.10, 0.09)
Gel 1% 125 mg/d		1.58 (0.08, 39.40)	1.52 (0.09, 15.81)	0.03 (-0.10, 0.59)
Gel 1.62% 40.5 mg/d		0.55 (0.06, 6.95)	0.56 (0.07, 5.62)	-0.02 (-0.12, 0.19)
Oral TU 160 mg/d		0.33 (0.06, 1.63)	0.35 (0.07, 1.60)	-0.04 (-0.13, 0.02)
IM TU 1000 mg/9 wk		2.16 (0.04, 170.20)	2.01 (0.04, 21.22)	0.06 (-0.10, 0.84)
IM TU 1000 mg/12 wk		0.25 (0.04, 1.28)	0.27 (0.05, 1.27)	-0.04 (-0.14, 0.01)
IM TE 250 mg/3 wk		1.23 (0.07, 24.17)	1.22 (0.07, 12.44)	0.01 (-0.11, 0.48)
Gel 1% 125 mg/d	Gel 1% 100 mg/d	1.61 (0.08, 40.83)	1.55 (0.09, 16.02)	0.03 (-0.10, 0.60)
Gel 1.62% 40.5 mg/d		0.56 (0.07, 7.01)	0.57 (0.07, 5.68)	-0.02 (-0.12, 0.18)
Oral TU 160 mg/d		0.33 (0.07, 1.73)	0.34 (0.07, 1.69)	-0.04 (-0.12, 0.02)
IM TU 1000 mg/9 wk		2.18 (0.04, 176.80)	2.03 (0.04, 21.78)	0.06 (-0.10, 0.84)
IM TU 1000 mg/12 wk		0.25 (0.05, 1.33)	0.26 (0.05, 1.32)	-0.04 (-0.13, 0.01)
IM TE 250 mg/3 wk		1.22 (0.07, 24.72)	1.20 (0.08, 12.54)	0.01 (-0.10, 0.48)
Gel 1.62% 40.5 mg/d	Gel 1% 125 mg/d	0.36 (0.01, 12.90)	0.39 (0.02, 11.02)	-0.05 (-0.61, 0.17)
Oral TU 160 mg/d		0.21 (0.01, 4.72)	0.23 (0.02, 4.56)	-0.07 (-0.63, 0.03)
IM TU 1000 mg/9 wk		1.35 (0.01, 241.90)	1.28 (0.02, 49.53)	0.02 (-0.54, 0.81)
IM TU 1000 mg/12 wk		0.16 (0.01, 3.51)	0.17 (0.01, 3.44)	-0.07 (-0.63, 0.02)
IM TE 250 mg/3 wk		0.78 (0.01, 42.05)	0.81 (0.03, 25.70)	-0.01 (-0.58, 0.45)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.61 (0.04, 5.42)	0.61 (0.05, 5.23)	-0.01 (-0.22, 0.04)
IM TU 1000 mg/9 wk		3.76 (0.04, 416.40)	3.31 (0.05, 66.40)	0.07 (-0.16, 0.86)
IM TU 1000 mg/12 wk		0.45 (0.03, 4.73)	0.46 (0.04, 4.59)	-0.02 (-0.22, 0.03)
IM TE 250 mg/3 wk		2.22 (0.06, 68.10)	2.10 (0.08, 37.47)	0.03 (-0.17, 0.50)
IM TU 1000 mg/9 wk	Oral TU 160 mg/d	6.70 (0.11, 549.70)	5.86 (0.12, 75.65)	0.10 (-0.04, 0.88)
IM TU 1000 mg/12 wk		0.76 (0.12, 4.68)	0.76 (0.12, 4.53)	0.00 (-0.05, 0.03)
IM TE 250 mg/3 wk		3.74 (0.19, 82.25)	3.52 (0.20, 42.56)	0.05 (-0.04, 0.52)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.12 (0.00, 6.24)	0.13 (0.01, 6.08)	-0.10 (-0.89, 0.02)
IM TE 250 mg/3 wk		0.62 (0.01, 17.18)	0.68 (0.04, 13.97)	-0.03 (-0.75, 0.27)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	5.08 (0.26, 108.80)	4.72 (0.26, 57.80)	0.05 (-0.02, 0.52)

Serious adverse events, continuity correction, treatments with zero events dropped — Odds Ratios, Relative Risks and Risk Difference (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	1.66 (0.14, 19.53)	1.61 (0.14, 11.44)	0.03 (-0.04, 0.41)
Gel 1% 50 mg/d		1.33 (0.48, 3.76)	1.31 (0.49, 3.38)	0.01 (-0.02, 0.10)
Gel 1% 100 mg/d		1.33 (0.48, 3.40)	1.31 (0.49, 3.08)	0.01 (-0.02, 0.09)
Gel 1% 125 mg/d		2.28 (0.11, 56.36)	2.15 (0.12, 18.62)	0.05 (-0.05, 0.65)
Gel 1.62% 40.5 mg/d		0.72 (0.12, 7.30)	0.73 (0.13, 5.85)	-0.01 (-0.05, 0.19)
Oral TU 160 mg/d		0.45 (0.12, 1.60)	0.46 (0.12, 1.56)	-0.02 (-0.05, 0.02)
IM TU 1000 mg/12 wk		0.34 (0.08, 1.25)	0.35 (0.09, 1.23)	-0.03 (-0.05, 0.01)
IM TE 250 mg/3 wk		2.52 (0.15, 38.99)	2.36 (0.16, 15.65)	0.06 (-0.04, 0.58)
Gel 1% 50 mg/d	Patch 5 mg/d	0.80 (0.05, 12.13)	0.81 (0.09, 10.98)	-0.01 (-0.39, 0.11)
Gel 1% 100 mg/d		0.79 (0.06, 11.70)	0.80 (0.09, 10.75)	-0.01 (-0.39, 0.10)
Gel 1% 125 mg/d		1.36 (0.03, 68.85)	1.31 (0.04, 31.86)	0.02 (-0.36, 0.61)
Gel 1.62% 40.5 mg/d		0.46 (0.02, 11.54)	0.48 (0.03, 9.72)	-0.03 (-0.41, 0.16)
Oral TU 160 mg/d		0.27 (0.02, 4.41)	0.28 (0.03, 4.25)	-0.05 (-0.42, 0.03)
IM TU 1000 mg/12 wk		0.20 (0.01, 3.22)	0.22 (0.02, 3.15)	-0.05 (-0.43, 0.02)
IM TE 250 mg/3 wk		1.56 (0.27, 6.87)	1.45 (0.29, 5.17)	0.02 (-0.11, 0.32)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.01 (0.23, 3.95)	1.01 (0.26, 3.63)	0.00 (-0.10, 0.09)
Gel 1% 125 mg/d		1.69 (0.07, 46.82)	1.62 (0.08, 17.41)	0.03 (-0.10, 0.63)
Gel 1.62% 40.5 mg/d		0.55 (0.07, 6.84)	0.57 (0.08, 5.59)	-0.02 (-0.12, 0.18)
Oral TU 160 mg/d		0.34 (0.06, 1.74)	0.35 (0.07, 1.70)	-0.04 (-0.13, 0.02)
IM TU 1000 mg/12 wk		0.26 (0.05, 1.34)	0.27 (0.05, 1.32)	-0.04 (-0.13, 0.01)
IM TE 250 mg/3 wk		1.90 (0.10, 35.81)	1.79 (0.11, 15.82)	0.04 (-0.10, 0.57)
Gel 1% 125 mg/d	Gel 1% 100 mg/d	1.73 (0.07, 47.51)	1.66 (0.08, 17.09)	0.04 (-0.10, 0.63)
Gel 1.62% 40.5 mg/d		0.56 (0.07, 6.56)	0.57 (0.08, 5.38)	-0.02 (-0.11, 0.18)
Oral TU 160 mg/d		0.34 (0.07, 1.79)	0.35 (0.07, 1.74)	-0.04 (-0.12, 0.02)
IM TU 1000 mg/12 wk		0.25 (0.05, 1.38)	0.27 (0.05, 1.36)	-0.04 (-0.12, 0.01)
IM TE 250 mg/3 wk		1.90 (0.10, 35.41)	1.79 (0.11, 15.49)	0.04 (-0.09, 0.57)
Gel 1.62% 40.5 mg/d	Gel 1% 125 mg/d	0.34 (0.01, 14.03)	0.37 (0.02, 11.92)	-0.05 (-0.65, 0.16)
Oral TU 160 mg/d		0.20 (0.01, 4.96)	0.22 (0.02, 4.78)	-0.07 (-0.67, 0.03)
IM TU 1000 mg/12 wk		0.15 (0.00, 4.00)	0.16 (0.01, 3.90)	-0.08 (-0.67, 0.02)
IM TE 250 mg/3 wk		1.11 (0.02, 56.53)	1.09 (0.04, 32.09)	0.01 (-0.58, 0.53)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.60 (0.04, 5.65)	0.61 (0.05, 5.42)	-0.01 (-0.21, 0.04)
IM TU 1000 mg/12 wk		0.46 (0.03, 4.37)	0.47 (0.04, 4.25)	-0.02 (-0.22, 0.03)
IM TE 250 mg/3 wk		3.28 (0.10, 92.76)	2.99 (0.12, 44.31)	0.06 (-0.14, 0.58)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.76 (0.12, 4.70)	0.76 (0.13, 4.56)	0.00 (-0.05, 0.03)
IM TE 250 mg/3 wk		5.61 (0.26, 118.40)	5.05 (0.27, 53.86)	0.08 (-0.03, 0.60)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	7.44 (0.34, 160.40)	6.65 (0.34, 70.56)	0.09 (-0.02, 0.60)

Withdrawals due to adverse events, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	2.71 (0.69, 9.34)	2.56 (0.70, 7.32)	0.05 (-0.01, 0.21)
Gel 1% 5 mg/d		0.83 (0.28, 2.81)	0.83 (0.28, 2.64)	-0.01 (-0.03, 0.06)
Gel 1% 50 mg/d		0.85 (0.38, 1.65)	0.85 (0.39, 1.62)	-0.01 (-0.02, 0.02)
Gel 1% 75 mg/d		3.61 (0.42, 40.86)	3.31 (0.42, 17.56)	0.08 (-0.02, 0.56)

Gel 1%, 100 mg/wk		0.78 (0.27, 1.91)	0.78 (0.28, 1.85)	-0.01 (-0.03, 0.03)
Gel 1.62% 40.5 mg/d		9.83 (1.08, 193.30)	7.49 (1.07, 27.56)	0.23 (0.00, 0.83)
Gel 2% 60 mg/d		1.61 (0.45, 5.80)	1.57 (0.45, 4.99)	0.02 (-0.02, 0.14)
Oral TU 120 mg/d		0.21 (0.00, 14.06)	0.22 (0.00, 9.84)	-0.03 (-0.04, 0.29)
Oral TU 160 mg/d		1.01 (0.33, 3.39)	1.01 (0.33, 3.14)	0.00 (-0.02, 0.07)
Oral TU 120-160 mg/d		0.21 (0.00, 11.24)	0.21 (0.00, 8.38)	-0.03 (-0.04, 0.25)
IM TU 1000 mg/9 wk		9.07 (0.08, 1830.00)	7.08 (0.08, 32.00)	0.21 (-0.03, 0.95)
IM TU 1000 mg/12 wk		0.37 (0.12, 1.09)	0.38 (0.12, 1.09)	-0.02 (-0.04, 0.00)
IM TE 100 mg/wk		0.19 (0.00, 17.08)	0.20 (0.00, 11.14)	-0.03 (-0.04, 0.34)
IM TE 125 mg/wk		6.20 (0.76, 60.80)	5.25 (0.76, 20.51)	0.15 (-0.01, 0.65)
IM TE 150 mg/2 wk		0.72 (0.04, 12.02)	0.73 (0.04, 8.79)	-0.01 (-0.04, 0.26)
IM TE 200 mg/2wk		2.59 (0.59, 12.46)	2.45 (0.60, 9.08)	0.05 (-0.01, 0.26)
IM TE 250 mg/3wk		3.99 (0.36, 69.56)	3.61 (0.37, 21.82)	0.09 (-0.02, 0.67)
IM TE 250 mg/4 wk		1.56 (0.12, 18.91)	1.53 (0.13, 11.76)	0.02 (-0.03, 0.36)
IM TE 300 mg/3wk		0.69 (0.10, 4.69)	0.70 (0.10, 4.17)	-0.01 (-0.03, 0.11)
IM TE 50-400 mg/wk		0.26 (0.00, 22.45)	0.27 (0.00, 13.22)	-0.02 (-0.04, 0.40)
IM TC 200 mg/2 wk		4.24 (0.54, 49.04)	3.81 (0.55, 18.97)	0.10 (-0.02, 0.59)
Gel 1% 5 mg/d	Patch 5 mg/d	0.31 (0.06, 2.05)	0.33 (0.08, 1.98)	-0.06 (-0.22, 0.03)
Gel 1% 50 mg/d		0.31 (0.09, 1.20)	0.33 (0.11, 1.19)	-0.06 (-0.21, 0.01)
Gel 1% 75 mg/d		1.37 (0.12, 21.00)	1.32 (0.14, 10.38)	0.03 (-0.16, 0.50)
Gel 1%, 100 mg/wk		0.29 (0.07, 1.20)	0.31 (0.09, 1.19)	-0.06 (-0.21, 0.01)
Gel 1.62% 40.5 mg/d		3.77 (0.29, 91.94)	2.95 (0.33, 18.67)	0.16 (-0.11, 0.78)
Gel 2% 60 mg/d		0.59 (0.11, 4.11)	0.62 (0.13, 3.62)	-0.03 (-0.19, 0.10)
Oral TU 120 mg/d		0.08 (0.00, 6.73)	0.09 (0.00, 5.02)	-0.07 (-0.23, 0.24)
Oral TU 160 mg/d		0.37 (0.07, 2.40)	0.40 (0.09, 2.28)	-0.05 (-0.21, 0.05)
Oral TU 120-160 mg/d		0.08 (0.00, 5.29)	0.09 (0.00, 4.17)	-0.07 (-0.23, 0.19)
IM TU 1000 mg/9 wk		3.42 (0.03, 834.50)	2.73 (0.03, 23.57)	0.15 (-0.16, 0.91)
IM TU 1000 mg/12 wk		0.14 (0.03, 0.78)	0.15 (0.03, 0.78)	-0.07 (-0.23, -0.01)
IM TE 100 mg/wk		0.07 (0.00, 8.27)	0.08 (0.00, 5.70)	-0.07 (-0.23, 0.28)
IM TE 125 mg/wk		2.34 (0.21, 33.67)	2.07 (0.24, 13.90)	0.09 (-0.13, 0.59)
IM TE 150 mg/2 wk		0.27 (0.01, 6.13)	0.29 (0.01, 4.71)	-0.05 (-0.22, 0.21)
IM TE 200 mg/2wk		0.97 (0.16, 6.48)	0.98 (0.19, 5.22)	0.00 (-0.16, 0.20)
IM TE 250 mg/3wk		1.52 (0.10, 34.89)	1.45 (0.12, 12.98)	0.03 (-0.16, 0.61)
IM TE 250 mg/4 wk		0.59 (0.03, 9.71)	0.62 (0.04, 6.58)	-0.03 (-0.20, 0.31)
IM TE 300 mg/3wk		0.26 (0.03, 2.76)	0.28 (0.03, 2.53)	-0.06 (-0.22, 0.07)
IM TE 50-400 mg/wk		0.10 (0.00, 9.92)	0.11 (0.00, 6.13)	-0.06 (-0.23, 0.34)
IM TC 200 mg/2 wk		1.60 (0.14, 26.24)	1.51 (0.16, 12.06)	0.04 (-0.16, 0.54)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.02 (0.23, 3.58)	1.02 (0.24, 3.47)	0.00 (-0.06, 0.03)
Gel 1% 75 mg/d		4.31 (0.37, 60.78)	3.89 (0.38, 28.97)	0.08 (-0.03, 0.56)
Gel 1%, 100 mg/wk		0.94 (0.18, 3.70)	0.95 (0.19, 3.58)	0.00 (-0.07, 0.04)
Gel 1.62% 40.5 mg/d		11.96 (0.96, 276.10)	8.80 (0.96, 49.30)	0.23 (0.00, 0.84)
Gel 2% 60 mg/d		1.95 (0.32, 10.28)	1.89 (0.34, 8.99)	0.02 (-0.05, 0.14)
Oral TU 120 mg/d		0.25 (0.00, 18.26)	0.26 (0.00, 12.95)	-0.02 (-0.08, 0.29)
Oral TU 160 mg/d		1.22 (0.24, 6.15)	1.21 (0.25, 5.73)	0.01 (-0.06, 0.08)
Oral TU 120-160 mg/d		0.25 (0.00, 15.29)	0.25 (0.00, 11.49)	-0.02 (-0.08, 0.25)
IM TU 1000 mg/9 wk		11.01 (0.08, 2415.00)	8.12 (0.08, 60.74)	0.21 (-0.04, 0.95)
IM TU 1000 mg/12 wk		0.44 (0.08, 2.09)	0.45 (0.09, 2.06)	-0.01 (-0.08, 0.01)
IM TE 100 mg/wk		0.23 (0.00, 23.01)	0.23 (0.00, 14.99)	-0.02 (-0.08, 0.34)
IM TE 125 mg/wk		7.51 (0.65, 90.95)	6.19 (0.66, 34.99)	0.15 (-0.02, 0.65)
IM TE 150 mg/2 wk		0.86 (0.03, 17.29)	0.86 (0.04, 12.77)	0.00 (-0.07, 0.26)

IM TE 200 mg/2wk		3.13 (0.45, 20.84)	2.93 (0.47, 15.68)	0.05 (-0.03, 0.27)
IM TE 250 mg/3wk		4.87 (0.33, 106.70)	4.34 (0.34, 36.25)	0.09 (-0.04, 0.68)
IM TE 250 mg/4 wk		1.87 (0.12, 28.50)	1.82 (0.12, 18.33)	0.02 (-0.06, 0.37)
IM TE 300 mg/3wk		0.83 (0.09, 7.36)	0.83 (0.09, 6.57)	0.00 (-0.07, 0.11)
IM TE 50-400 mg/wk		0.30 (0.00, 30.85)	0.31 (0.00, 17.90)	-0.02 (-0.08, 0.40)
IM TC 200 mg/2 wk		5.13 (0.46, 71.98)	4.54 (0.48, 31.46)	0.10 (-0.03, 0.60)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	4.31 (0.46, 56.28)	3.91 (0.47, 24.88)	0.08 (-0.02, 0.56)
Gel 1%, 100 mg/wk		0.92 (0.29, 2.86)	0.92 (0.30, 2.77)	0.00 (-0.03, 0.04)
Gel 1.62% 40.5 mg/d		11.78 (1.19, 248.70)	8.81 (1.19, 40.40)	0.23 (0.01, 0.84)
Gel 2% 60 mg/d		1.90 (0.48, 8.88)	1.85 (0.48, 7.62)	0.02 (-0.02, 0.15)
Oral TU 120 mg/d		0.25 (0.00, 17.70)	0.26 (0.00, 12.46)	-0.02 (-0.05, 0.29)
Oral TU 160 mg/d		1.20 (0.33, 5.32)	1.19 (0.34, 4.90)	0.01 (-0.03, 0.08)
Oral TU 120-160 mg/d		0.25 (0.00, 14.86)	0.25 (0.00, 11.05)	-0.02 (-0.05, 0.25)
IM TU 1000 mg/9 wk		10.83 (0.09, 2289.00)	8.23 (0.09, 48.86)	0.21 (-0.03, 0.95)
IM TU 1000 mg/12 wk		0.44 (0.11, 1.67)	0.44 (0.12, 1.65)	-0.02 (-0.05, 0.01)
IM TE 100 mg/wk		0.23 (0.00, 22.83)	0.24 (0.00, 14.64)	-0.02 (-0.05, 0.34)
IM TE 125 mg/wk		7.41 (0.83, 80.81)	6.16 (0.84, 29.19)	0.15 (-0.01, 0.65)
IM TE 150 mg/2 wk		0.86 (0.04, 15.80)	0.87 (0.04, 11.44)	0.00 (-0.04, 0.27)
IM TE 200 mg/2wk		3.08 (0.62, 17.25)	2.89 (0.63, 12.89)	0.05 (-0.01, 0.27)
IM TE 250 mg/3wk		4.81 (0.40, 95.06)	4.31 (0.41, 30.61)	0.09 (-0.02, 0.68)
IM TE 250 mg/4 wk		1.86 (0.13, 25.07)	1.81 (0.14, 15.78)	0.02 (-0.04, 0.37)
IM TE 300 mg/3wk		0.82 (0.11, 6.63)	0.82 (0.11, 5.86)	0.00 (-0.04, 0.11)
IM TE 50-400 mg/wk		0.31 (0.00, 28.23)	0.31 (0.00, 16.30)	-0.02 (-0.05, 0.40)
IM TC 200 mg/2 wk		5.05 (0.58, 68.06)	4.49 (0.60, 27.06)	0.10 (-0.01, 0.60)
Gel 1%, 100 mg/wk	Gel 1% 75 mg/d	0.21 (0.02, 2.22)	0.24 (0.03, 2.16)	-0.09 (-0.56, 0.02)
Gel 1.62% 40.5 mg/d		2.87 (0.10, 109.00)	2.24 (0.17, 27.38)	0.13 (-0.39, 0.76)
Gel 2% 60 mg/d		0.44 (0.03, 5.45)	0.48 (0.06, 4.94)	-0.06 (-0.53, 0.10)
Oral TU 120 mg/d		0.05 (0.00, 6.81)	0.07 (0.00, 5.21)	-0.09 (-0.56, 0.21)
Oral TU 160 mg/d		0.28 (0.02, 3.42)	0.31 (0.04, 3.25)	-0.08 (-0.55, 0.05)
Oral TU 120-160 mg/d		0.05 (0.00, 5.58)	0.06 (0.00, 4.41)	-0.09 (-0.57, 0.17)
IM TU 1000 mg/9 wk		2.45 (0.01, 683.80)	1.93 (0.02, 32.06)	0.10 (-0.44, 0.90)
IM TU 1000 mg/12 wk		0.10 (0.01, 1.17)	0.12 (0.01, 1.17)	-0.10 (-0.58, 0.00)
IM TE 100 mg/wk		0.05 (0.00, 7.82)	0.06 (0.00, 5.36)	-0.09 (-0.57, 0.24)
IM TE 125 mg/wk		1.72 (0.07, 41.05)	1.55 (0.13, 19.35)	0.05 (-0.42, 0.56)
IM TE 150 mg/2 wk		0.20 (0.00, 6.59)	0.23 (0.01, 5.23)	-0.07 (-0.55, 0.18)
IM TE 200 mg/2wk		0.72 (0.04, 10.37)	0.75 (0.08, 8.39)	-0.03 (-0.51, 0.20)
IM TE 250 mg/3wk		1.15 (0.03, 39.95)	1.12 (0.06, 17.04)	0.01 (-0.47, 0.59)
IM TE 250 mg/4 wk		0.42 (0.01, 11.85)	0.46 (0.03, 8.42)	-0.05 (-0.52, 0.28)
IM TE 300 mg/3wk		0.19 (0.01, 3.53)	0.21 (0.02, 3.25)	-0.08 (-0.56, 0.07)
IM TE 50-400 mg/wk		0.07 (0.00, 10.28)	0.08 (0.00, 6.53)	-0.09 (-0.57, 0.32)
IM TC 200 mg/2 wk		1.19 (0.05, 32.88)	1.16 (0.08, 17.32)	0.01 (-0.46, 0.52)
Gel 1.62% 40.5 mg/d	Gel 1%, 100 mg/wk	12.78 (1.18, 293.00)	9.44 (1.17, 51.16)	0.23 (0.01, 0.84)
Gel 2% 60 mg/d		2.07 (0.45, 11.27)	2.01 (0.46, 9.77)	0.03 (-0.03, 0.15)
Oral TU 120 mg/d		0.27 (0.00, 20.85)	0.28 (0.00, 14.43)	-0.02 (-0.06, 0.29)
Oral TU 160 mg/d		1.31 (0.31, 6.72)	1.30 (0.32, 6.19)	0.01 (-0.04, 0.08)
Oral TU 120-160 mg/d		0.26 (0.00, 16.89)	0.27 (0.00, 12.49)	-0.02 (-0.06, 0.25)
IM TU 1000 mg/9 wk		11.66 (0.10, 2556.00)	8.80 (0.10, 62.18)	0.21 (-0.03, 0.96)
IM TU 1000 mg/12 wk		0.47 (0.11, 2.14)	0.48 (0.11, 2.11)	-0.01 (-0.05, 0.02)
IM TE 100 mg/wk		0.25 (0.00, 25.53)	0.26 (0.00, 16.55)	-0.02 (-0.06, 0.34)
IM TE 125 mg/wk		7.96 (0.83, 100.30)	6.58 (0.84, 38.19)	0.15 (-0.01, 0.65)

IM TE 150 mg/2 wk		0.93 (0.04, 19.39)	0.93 (0.04, 14.11)	0.00 (-0.05, 0.27)
IM TE 200 mg/2wk		3.37 (0.61, 21.55)	3.15 (0.62, 16.17)	0.06 (-0.02, 0.27)
IM TE 250 mg/3wk		5.31 (0.41, 107.60)	4.71 (0.42, 35.21)	0.10 (-0.02, 0.67)
IM TE 250 mg/4 wk		2.02 (0.14, 30.25)	1.96 (0.15, 19.33)	0.02 (-0.04, 0.37)
IM TE 300 mg/3wk		0.89 (0.11, 8.03)	0.89 (0.11, 7.17)	0.00 (-0.05, 0.12)
IM TE 50-400 mg/wk		0.33 (0.00, 33.32)	0.34 (0.00, 19.28)	-0.01 (-0.06, 0.41)
IM TC 200 mg/2 wk		5.52 (0.58, 79.53)	4.87 (0.59, 32.87)	0.10 (-0.02, 0.60)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.16 (0.01, 2.09)	0.21 (0.03, 1.95)	-0.20 (-0.81, 0.05)
Oral TU 120 mg/d		0.02 (0.00, 2.44)	0.03 (0.00, 2.00)	-0.23 (-0.84, 0.11)
Oral TU 160 mg/d		0.10 (0.00, 1.36)	0.14 (0.02, 1.33)	-0.22 (-0.83, 0.01)
Oral TU 120-160 mg/d		0.02 (0.00, 2.09)	0.03 (0.00, 1.80)	-0.23 (-0.84, 0.08)
IM TU 1000 mg/9 wk		0.89 (0.00, 281.70)	0.93 (0.01, 12.81)	-0.01 (-0.73, 0.83)
IM TU 1000 mg/12 wk		0.04 (0.00, 0.45)	0.05 (0.01, 0.47)	-0.25 (-0.85, -0.02)
IM TE 100 mg/wk		0.02 (0.00, 2.67)	0.03 (0.00, 2.09)	-0.23 (-0.84, 0.14)
IM TE 125 mg/wk		0.61 (0.02, 15.31)	0.70 (0.07, 7.33)	-0.07 (-0.70, 0.48)
IM TE 150 mg/2 wk		0.07 (0.00, 2.87)	0.10 (0.00, 2.41)	-0.22 (-0.82, 0.12)
IM TE 200 mg/2wk		0.26 (0.01, 3.90)	0.33 (0.04, 3.31)	-0.16 (-0.78, 0.14)
IM TE 250 mg/3wk		0.39 (0.01, 16.12)	0.49 (0.04, 7.01)	-0.11 (-0.74, 0.50)
IM TE 250 mg/4 wk		0.15 (0.00, 4.43)	0.21 (0.01, 3.43)	-0.19 (-0.80, 0.20)
IM TE 300 mg/3wk		0.07 (0.00, 1.32)	0.10 (0.01, 1.29)	-0.23 (-0.83, 0.02)
IM TE 50-400 mg/wk		0.02 (0.00, 4.15)	0.04 (0.00, 2.90)	-0.22 (-0.84, 0.21)
IM TC 200 mg/2 wk		0.43 (0.01, 10.74)	0.53 (0.05, 5.94)	-0.11 (-0.74, 0.41)
Oral TU 120 mg/d	Gel 2% 60 mg/d	0.13 (0.00, 10.58)	0.14 (0.00, 7.38)	-0.04 (-0.16, 0.26)
Oral TU 160 mg/d		0.63 (0.11, 3.63)	0.64 (0.13, 3.42)	-0.02 (-0.14, 0.06)
Oral TU 120-160 mg/d		0.13 (0.00, 8.41)	0.13 (0.00, 6.27)	-0.04 (-0.16, 0.22)
IM TU 1000 mg/9 wk		5.69 (0.04, 1336.00)	4.30 (0.05, 35.24)	0.18 (-0.10, 0.93)
IM TU 1000 mg/12 wk		0.23 (0.04, 1.22)	0.24 (0.05, 1.22)	-0.04 (-0.16, 0.00)
IM TE 100 mg/wk		0.12 (0.00, 12.83)	0.12 (0.00, 8.51)	-0.04 (-0.16, 0.31)
IM TE 125 mg/wk		3.88 (0.33, 52.80)	3.29 (0.36, 20.88)	0.12 (-0.07, 0.62)
IM TE 150 mg/2 wk		0.44 (0.02, 9.70)	0.46 (0.02, 7.21)	-0.02 (-0.15, 0.24)
IM TE 200 mg/2wk		1.61 (0.23, 11.98)	1.55 (0.26, 9.30)	0.03 (-0.10, 0.24)
IM TE 250 mg/3wk		2.49 (0.16, 56.55)	2.28 (0.18, 19.89)	0.06 (-0.10, 0.65)
IM TE 250 mg/4 wk		0.96 (0.06, 16.20)	0.96 (0.07, 10.72)	0.00 (-0.12, 0.34)
IM TE 300 mg/3wk		0.43 (0.04, 4.22)	0.44 (0.05, 3.83)	-0.03 (-0.15, 0.09)
IM TE 50-400 mg/wk		0.16 (0.00, 16.98)	0.17 (0.00, 9.85)	-0.04 (-0.16, 0.37)
IM TC 200 mg/2 wk		2.61 (0.24, 41.97)	2.37 (0.26, 19.06)	0.07 (-0.09, 0.57)
Oral TU 160 mg/d	Oral TU 120 mg/d	4.80 (0.06, 1175.00)	4.64 (0.09, 1122.00)	0.02 (-0.29, 0.09)
Oral TU 120-160 mg/d		1.01 (0.00, 725.30)	1.01 (0.00, 623.10)	0.00 (-0.29, 0.26)
IM TU 1000 mg/9 wk		50.07 (0.08, 59760.00)	26.50 (0.10, 8183.00)	0.21 (-0.14, 0.97)
IM TU 1000 mg/12 wk		1.73 (0.02, 441.40)	1.72 (0.04, 434.00)	0.00 (-0.31, 0.03)
IM TE 100 mg/wk		0.99 (0.00, 685.90)	0.99 (0.00, 512.00)	0.00 (-0.29, 0.35)
IM TE 125 mg/wk		30.25 (0.29, 10200.00)	22.97 (0.37, 5907.00)	0.15 (-0.15, 0.66)
IM TE 150 mg/2 wk		3.66 (0.02, 1450.00)	3.53 (0.03, 1250.00)	0.01 (-0.27, 0.28)
IM TE 200 mg/2wk		12.62 (0.16, 3147.00)	11.34 (0.22, 2698.00)	0.06 (-0.23, 0.28)
IM TE 250 mg/3wk		20.98 (0.17, 7124.00)	16.77 (0.22, 4239.00)	0.10 (-0.18, 0.68)
IM TE 250 mg/4 wk		7.52 (0.06, 2801.00)	6.94 (0.08, 2316.00)	0.03 (-0.25, 0.38)
IM TE 300 mg/3wk		3.30 (0.03, 1012.00)	3.22 (0.05, 944.20)	0.01 (-0.29, 0.13)
IM TE 50-400 mg/wk		1.33 (0.00, 867.40)	1.32 (0.00, 686.60)	0.00 (-0.29, 0.41)
IM TC 200 mg/2 wk		21.67 (0.19, 8290.00)	17.63 (0.25, 5466.00)	0.11 (-0.19, 0.61)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.20 (0.00, 13.52)	0.21 (0.00, 10.04)	-0.02 (-0.09, 0.24)

IM TU 1000 mg/9 wk		8.71 (0.07, 1877.00)	6.56 (0.07, 52.74)	0.20 (-0.05, 0.95)
IM TU 1000 mg/12 wk		0.36 (0.07, 1.79)	0.37 (0.07, 1.77)	-0.02 (-0.09, 0.01)
IM TE 100 mg/wk		0.19 (0.00, 19.77)	0.20 (0.00, 13.07)	-0.02 (-0.09, 0.34)
IM TE 125 mg/wk		6.15 (0.53, 80.78)	5.11 (0.55, 31.34)	0.14 (-0.03, 0.64)
IM TE 150 mg/2 wk		0.72 (0.03, 14.20)	0.73 (0.03, 10.51)	-0.01 (-0.08, 0.26)
IM TE 200 mg/2wk		2.57 (0.37, 16.98)	2.42 (0.39, 13.09)	0.05 (-0.05, 0.26)
IM TE 250 mg/3wk		4.01 (0.27, 86.72)	3.58 (0.28, 29.85)	0.09 (-0.05, 0.67)
IM TE 250 mg/4 wk		1.53 (0.09, 24.23)	1.50 (0.10, 15.96)	0.02 (-0.07, 0.36)
IM TE 300 mg/3wk		0.67 (0.07, 6.25)	0.68 (0.08, 5.58)	-0.01 (-0.08, 0.11)
IM TE 50-400 mg/wk		0.25 (0.00, 24.81)	0.26 (0.00, 14.55)	-0.02 (-0.09, 0.39)
IM TC 200 mg/2 wk		4.21 (0.37, 62.76)	3.74 (0.39, 27.03)	0.09 (-0.04, 0.59)
IM TU 1000 mg/9 wk	Oral TU 120-160 mg/d	54.11 (0.09, 63000.00)	28.07 (0.11, 8291.00)	0.21 (-0.13, 0.97)
IM TU 1000 mg/12 wk		1.80 (0.03, 402.00)	1.79 (0.04, 396.00)	0.00 (-0.27, 0.03)
IM TE 100 mg/wk		1.01 (0.00, 1841.00)	1.01 (0.00, 1260.00)	0.00 (-0.26, 0.35)
IM TE 125 mg/wk		31.97 (0.28, 10330.00)	24.05 (0.35, 6223.00)	0.16 (-0.14, 0.66)
IM TE 150 mg/2 wk		3.82 (0.02, 1518.00)	3.68 (0.03, 1284.00)	0.01 (-0.24, 0.28)
IM TE 200 mg/2wk		12.84 (0.17, 3321.00)	11.61 (0.22, 2814.00)	0.06 (-0.19, 0.28)
IM TE 250 mg/3wk		21.69 (0.19, 10280.00)	17.23 (0.24, 5877.00)	0.10 (-0.15, 0.69)
IM TE 250 mg/4 wk		8.27 (0.06, 2768.00)	7.62 (0.08, 2261.00)	0.03 (-0.22, 0.38)
IM TE 300 mg/3wk		3.51 (0.04, 988.70)	3.42 (0.05, 922.70)	0.01 (-0.25, 0.13)
IM TE 50-400 mg/wk		1.39 (0.00, 1434.00)	1.38 (0.00, 1024.00)	0.00 (-0.25, 0.41)
IM TC 200 mg/2 wk		23.29 (0.22, 6149.00)	18.57 (0.27, 4175.00)	0.11 (-0.16, 0.60)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.04 (0.00, 4.74)	0.06 (0.01, 4.66)	-0.23 (-0.97, 0.01)
IM TE 100 mg/wk		0.02 (0.00, 12.26)	0.04 (0.00, 9.26)	-0.21 (-0.97, 0.18)
IM TE 125 mg/wk		0.68 (0.00, 124.00)	0.77 (0.06, 73.65)	-0.05 (-0.86, 0.52)
IM TE 150 mg/2 wk		0.08 (0.00, 17.88)	0.12 (0.00, 15.53)	-0.19 (-0.95, 0.14)
IM TE 200 mg/2wk		0.28 (0.00, 42.36)	0.36 (0.04, 35.42)	-0.15 (-0.91, 0.20)
IM TE 250 mg/3wk		0.48 (0.00, 50.85)	0.62 (0.04, 33.57)	-0.08 (-0.86, 0.41)
IM TE 250 mg/4 wk		0.17 (0.00, 32.54)	0.25 (0.01, 26.66)	-0.16 (-0.94, 0.24)
IM TE 300 mg/3wk		0.08 (0.00, 11.77)	0.11 (0.01, 11.05)	-0.21 (-0.96, 0.06)
IM TE 50-400 mg/wk		0.03 (0.00, 16.27)	0.05 (0.00, 12.60)	-0.20 (-0.97, 0.22)
IM TC 200 mg/2 wk		0.47 (0.00, 84.82)	0.59 (0.04, 55.65)	-0.09 (-0.88, 0.45)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	0.53 (0.00, 54.54)	0.53 (0.00, 34.34)	0.00 (-0.03, 0.36)
IM TE 125 mg/wk		17.10 (1.55, 222.00)	13.82 (1.53, 84.95)	0.17 (0.01, 0.67)
IM TE 150 mg/2 wk		1.97 (0.08, 39.71)	1.94 (0.08, 29.02)	0.01 (-0.02, 0.28)
IM TE 200 mg/2wk		7.07 (1.15, 51.76)	6.50 (1.15, 38.94)	0.07 (0.00, 0.29)
IM TE 250 mg/3wk		11.02 (0.78, 245.80)	9.64 (0.78, 82.51)	0.11 (0.00, 0.69)
IM TE 250 mg/4 wk		4.27 (0.27, 64.61)	4.07 (0.28, 42.06)	0.04 (-0.02, 0.38)
IM TE 300 mg/3wk		1.86 (0.20, 17.12)	1.84 (0.21, 15.05)	0.01 (-0.02, 0.13)
IM TE 50-400 mg/wk		0.70 (0.00, 69.03)	0.70 (0.00, 39.78)	0.00 (-0.03, 0.42)
IM TC 200 mg/2 wk		11.88 (1.09, 163.80)	10.28 (1.08, 72.15)	0.12 (0.00, 0.61)
IM TE 125 mg/wk	IM TE 100 mg/wk	35.32 (0.23, 12740.00)	26.27 (0.30, 8048.00)	0.15 (-0.20, 0.66)
IM TE 150 mg/2 wk		3.68 (0.02, 2014.00)	3.54 (0.03, 1738.00)	0.01 (-0.33, 0.28)
IM TE 200 mg/2wk		14.04 (0.11, 4764.00)	12.57 (0.16, 4104.00)	0.07 (-0.28, 0.28)
IM TE 250 mg/3wk		23.47 (0.14, 9643.00)	18.64 (0.19, 5835.00)	0.10 (-0.23, 0.69)
IM TE 250 mg/4 wk		8.71 (0.04, 3421.00)	7.96 (0.06, 2892.00)	0.03 (-0.32, 0.37)
IM TE 300 mg/3wk		3.69 (0.03, 1434.00)	3.60 (0.04, 1353.00)	0.01 (-0.34, 0.13)
IM TE 50-400 mg/wk		1.47 (0.00, 1428.00)	1.45 (0.00, 1064.00)	0.00 (-0.34, 0.40)
IM TC 200 mg/2 wk		23.49 (0.14, 8580.00)	18.97 (0.21, 5938.00)	0.11 (-0.25, 0.60)

IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.11 (0.00, 3.73)	0.14 (0.01, 3.09)	-0.14 (-0.64, 0.14)
IM TE 200 mg/2wk		0.41 (0.03, 5.91)	0.47 (0.06, 4.83)	-0.09 (-0.59, 0.18)
IM TE 250 mg/3wk		0.66 (0.02, 22.82)	0.71 (0.05, 9.76)	-0.04 (-0.56, 0.55)
IM TE 250 mg/4 wk		0.25 (0.01, 6.55)	0.30 (0.02, 4.71)	-0.11 (-0.62, 0.24)
IM TE 300 mg/3wk		0.11 (0.01, 1.86)	0.14 (0.01, 1.77)	-0.15 (-0.64, 0.03)
IM TE 50-400 mg/wk		0.04 (0.00, 5.46)	0.05 (0.00, 3.68)	-0.15 (-0.66, 0.24)
IM TC 200 mg/2 wk		0.68 (0.03, 16.72)	0.74 (0.07, 8.74)	-0.04 (-0.55, 0.46)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.63 (0.15, 106.90)	3.37 (0.20, 87.57)	0.05 (-0.21, 0.26)
IM TE 250 mg/3wk		5.65 (0.14, 356.30)	4.82 (0.18, 161.60)	0.08 (-0.18, 0.67)
IM TE 250 mg/4 wk		2.13 (0.05, 108.10)	2.04 (0.07, 77.68)	0.02 (-0.23, 0.36)
IM TE 300 mg/3wk		0.97 (0.03, 31.21)	0.97 (0.04, 28.87)	0.00 (-0.27, 0.11)
IM TE 50-400 mg/wk		0.37 (0.00, 70.08)	0.38 (0.00, 44.70)	-0.01 (-0.27, 0.39)
IM TC 200 mg/2 wk		6.00 (0.19, 287.10)	5.11 (0.24, 155.10)	0.09 (-0.17, 0.59)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.58 (0.09, 35.45)	1.49 (0.12, 13.54)	0.04 (-0.20, 0.61)
IM TE 250 mg/4 wk		0.60 (0.03, 10.93)	0.62 (0.04, 7.40)	-0.03 (-0.24, 0.31)
IM TE 300 mg/3wk		0.27 (0.02, 3.00)	0.29 (0.03, 2.75)	-0.05 (-0.27, 0.07)
IM TE 50-400 mg/wk		0.10 (0.00, 11.11)	0.11 (0.00, 6.61)	-0.06 (-0.27, 0.35)
IM TC 200 mg/2 wk		1.65 (0.13, 29.08)	1.55 (0.15, 13.45)	0.04 (-0.19, 0.54)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.38 (0.01, 11.94)	0.42 (0.02, 8.82)	-0.06 (-0.64, 0.27)
IM TE 300 mg/3wk		0.17 (0.01, 3.93)	0.19 (0.01, 3.64)	-0.09 (-0.67, 0.07)
IM TE 50-400 mg/wk		0.06 (0.00, 8.67)	0.08 (0.00, 5.81)	-0.09 (-0.67, 0.29)
IM TC 200 mg/2 wk		1.08 (0.03, 31.66)	1.07 (0.07, 16.99)	0.01 (-0.59, 0.50)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.43 (0.02, 10.80)	0.45 (0.03, 9.83)	-0.02 (-0.36, 0.09)
IM TE 50-400 mg/wk		0.16 (0.00, 24.32)	0.17 (0.00, 15.94)	-0.03 (-0.37, 0.36)
IM TC 200 mg/2 wk		2.79 (0.11, 93.18)	2.49 (0.15, 48.26)	0.06 (-0.27, 0.57)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.36 (0.00, 51.90)	0.37 (0.00, 31.03)	-0.01 (-0.12, 0.40)
IM TC 200 mg/2 wk		6.28 (0.35, 141.70)	5.39 (0.38, 68.91)	0.10 (-0.06, 0.60)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	17.41 (0.13, 5180.00)	14.29 (0.19, 3287.00)	0.10 (-0.28, 0.60)

Withdrawals due to adverse events, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	2.38 (0.79, 7.32)	2.22 (0.80, 5.60)	0.06 (-0.01, 0.23)
Gel 1% 5 mg/d		0.83 (0.32, 2.29)	0.84 (0.33, 2.14)	-0.01 (-0.04, 0.06)
Gel 1% 50 mg/d		0.88 (0.46, 1.63)	0.88 (0.47, 1.58)	-0.01 (-0.03, 0.03)
Gel 1% 75 mg/d		3.51 (0.44, 41.31)	3.10 (0.45, 13.68)	0.11 (-0.03, 0.64)
Gel 1%, 100 mg/wk		0.80 (0.32, 1.82)	0.81 (0.34, 1.75)	-0.01 (-0.04, 0.04)
Gel 1.62% 40.5 mg/d		9.51 (1.26, 155.90)	6.54 (1.24, 18.72)	0.29 (0.01, 0.84)
Gel 2% 60 mg/d		1.64 (0.53, 5.08)	1.59 (0.54, 4.19)	0.03 (-0.02, 0.17)
Oral TU 120 mg/d		0.61 (0.01, 15.56)	0.63 (0.01, 8.97)	-0.02 (-0.06, 0.40)
Oral TU 160 mg/d		1.02 (0.38, 2.89)	1.02 (0.39, 2.64)	0.00 (-0.03, 0.08)
Oral TU 120-160 mg/d		0.52 (0.01, 12.16)	0.53 (0.01, 7.74)	-0.02 (-0.06, 0.34)
IM TU 1000 mg/9 wk		4.69 (0.12, 254.20)	3.92 (0.13, 18.52)	0.15 (-0.05, 0.88)
IM TU 1000 mg/12 wk		0.45 (0.16, 1.16)	0.46 (0.17, 1.15)	-0.03 (-0.05, 0.01)
IM TE 100 mg/wk		0.55 (0.01, 12.87)	0.56 (0.02, 8.00)	-0.02 (-0.06, 0.36)
IM TE 125 mg/wk		6.16 (0.84, 55.57)	4.84 (0.85, 15.00)	0.20 (-0.01, 0.70)
IM TE 150 mg/2 wk		0.73 (0.04, 9.95)	0.74 (0.04, 6.79)	-0.01 (-0.06, 0.30)
IM TE 200 mg/2wk		2.38 (0.67, 9.40)	2.21 (0.68, 6.66)	0.06 (-0.02, 0.28)

IM TE 250 mg/3wk		3.27 (0.42, 37.44)	2.92 (0.44, 13.32)	0.10 (-0.03, 0.61)
IM TE 250 mg/4 wk		1.48 (0.14, 16.80)	1.45 (0.15, 9.30)	0.02 (-0.05, 0.43)
IM TE 300 mg/3wk		0.69 (0.11, 3.92)	0.70 (0.12, 3.40)	-0.02 (-0.05, 0.13)
IM TE 50-400 mg/wk		0.62 (0.02, 15.24)	0.63 (0.02, 8.85)	-0.02 (-0.06, 0.40)
IM TC 200 mg/2 wk		4.46 (0.60, 45.09)	3.76 (0.61, 13.91)	0.15 (-0.02, 0.66)
Gel 1% 5 mg/d	Patch 5 mg/d	0.35 (0.08, 1.68)	0.38 (0.10, 1.62)	-0.07 (-0.24, 0.03)
Gel 1% 50 mg/d		0.37 (0.11, 1.18)	0.40 (0.14, 1.17)	-0.07 (-0.23, 0.01)
Gel 1% 75 mg/d		1.48 (0.15, 20.66)	1.39 (0.17, 8.27)	0.04 (-0.17, 0.57)
Gel 1%, 100 mg/wk		0.33 (0.10, 1.14)	0.36 (0.12, 1.13)	-0.07 (-0.23, 0.01)
Gel 1.62% 40.5 mg/d		4.07 (0.40, 76.90)	2.90 (0.45, 12.78)	0.22 (-0.10, 0.78)
Gel 2% 60 mg/d		0.69 (0.14, 3.47)	0.71 (0.18, 3.01)	-0.03 (-0.21, 0.13)
Oral TU 120 mg/d		0.25 (0.00, 8.13)	0.28 (0.01, 4.95)	-0.07 (-0.25, 0.34)
Oral TU 160 mg/d		0.43 (0.10, 1.97)	0.46 (0.12, 1.86)	-0.06 (-0.23, 0.05)
Oral TU 120-160 mg/d		0.22 (0.00, 6.34)	0.24 (0.01, 4.26)	-0.08 (-0.25, 0.29)
IM TU 1000 mg/9 wk		1.92 (0.04, 121.10)	1.71 (0.05, 12.28)	0.08 (-0.19, 0.81)
IM TU 1000 mg/12 wk		0.18 (0.04, 0.81)	0.21 (0.05, 0.82)	-0.09 (-0.26, -0.01)
IM TE 100 mg/wk		0.23 (0.01, 6.99)	0.25 (0.01, 4.50)	-0.07 (-0.26, 0.30)
IM TE 125 mg/wk		2.58 (0.26, 31.05)	2.14 (0.31, 10.54)	0.13 (-0.14, 0.64)
IM TE 150 mg/2 wk		0.30 (0.01, 5.08)	0.33 (0.02, 3.71)	-0.07 (-0.25, 0.24)
IM TE 200 mg/2wk		1.01 (0.22, 4.94)	1.01 (0.26, 3.88)	0.00 (-0.17, 0.21)
IM TE 250 mg/3wk		1.38 (0.14, 20.97)	1.31 (0.16, 8.44)	0.03 (-0.18, 0.56)
IM TE 250 mg/4 wk		0.64 (0.04, 9.09)	0.67 (0.05, 5.54)	-0.03 (-0.23, 0.36)
IM TE 300 mg/3wk		0.29 (0.03, 2.27)	0.32 (0.04, 2.07)	-0.07 (-0.25, 0.08)
IM TE 50-400 mg/wk		0.26 (0.01, 7.83)	0.29 (0.01, 4.96)	-0.07 (-0.24, 0.34)
IM TC 200 mg/2 wk		1.87 (0.19, 25.42)	1.68 (0.22, 9.44)	0.08 (-0.16, 0.60)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.05 (0.31, 3.25)	1.05 (0.33, 3.10)	0.00 (-0.07, 0.05)
Gel 1% 75 mg/d		4.25 (0.41, 58.35)	3.67 (0.43, 21.42)	0.12 (-0.04, 0.64)
Gel 1%, 100 mg/wk		0.96 (0.24, 3.35)	0.96 (0.26, 3.18)	0.00 (-0.08, 0.05)
Gel 1.62% 40.5 mg/d		11.30 (1.17, 220.30)	7.49 (1.16, 32.72)	0.30 (0.01, 0.85)
Gel 2% 60 mg/d		1.98 (0.43, 8.36)	1.89 (0.45, 7.02)	0.04 (-0.05, 0.17)
Oral TU 120 mg/d		0.73 (0.01, 20.42)	0.74 (0.01, 12.01)	-0.01 (-0.09, 0.40)
Oral TU 160 mg/d		1.22 (0.30, 4.95)	1.20 (0.32, 4.51)	0.01 (-0.07, 0.09)
Oral TU 120-160 mg/d		0.61 (0.01, 17.44)	0.62 (0.01, 11.18)	-0.01 (-0.09, 0.35)
IM TU 1000 mg/9 wk		5.50 (0.13, 336.30)	4.46 (0.14, 30.10)	0.16 (-0.06, 0.89)
IM TU 1000 mg/12 wk		0.53 (0.12, 2.07)	0.54 (0.13, 2.01)	-0.02 (-0.09, 0.02)
IM TE 100 mg/wk		0.66 (0.02, 16.93)	0.67 (0.02, 10.62)	-0.01 (-0.09, 0.36)
IM TE 125 mg/wk		7.41 (0.76, 80.35)	5.64 (0.78, 25.22)	0.21 (-0.01, 0.70)
IM TE 150 mg/2 wk		0.87 (0.04, 14.03)	0.88 (0.04, 9.72)	0.00 (-0.09, 0.30)
IM TE 200 mg/2wk		2.86 (0.57, 14.99)	2.62 (0.60, 10.98)	0.07 (-0.03, 0.29)
IM TE 250 mg/3wk		3.92 (0.40, 50.54)	3.42 (0.42, 20.08)	0.11 (-0.04, 0.61)
IM TE 250 mg/4 wk		1.78 (0.14, 23.57)	1.71 (0.15, 13.85)	0.03 (-0.07, 0.43)
IM TE 300 mg/3wk		0.83 (0.10, 5.93)	0.83 (0.11, 5.15)	-0.01 (-0.08, 0.13)
IM TE 50-400 mg/wk		0.74 (0.02, 21.23)	0.75 (0.02, 12.45)	-0.01 (-0.09, 0.41)
IM TC 200 mg/2 wk		5.40 (0.53, 64.88)	4.45 (0.55, 22.65)	0.15 (-0.03, 0.66)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	4.05 (0.47, 51.49)	3.52 (0.49, 17.51)	0.12 (-0.03, 0.65)
Gel 1%, 100 mg/wk		0.91 (0.32, 2.50)	0.91 (0.33, 2.38)	0.00 (-0.05, 0.05)
Gel 1.62% 40.5 mg/d		11.03 (1.23, 186.40)	7.43 (1.21, 25.21)	0.30 (0.01, 0.84)
Gel 2% 60 mg/d		1.86 (0.53, 7.10)	1.79 (0.54, 5.87)	0.04 (-0.03, 0.18)
Oral TU 120 mg/d		0.70 (0.01, 19.06)	0.71 (0.02, 11.05)	-0.01 (-0.07, 0.41)
Oral TU 160 mg/d		1.15 (0.37, 4.09)	1.14 (0.39, 3.71)	0.01 (-0.04, 0.09)

Oral TU 120-160 mg/d		0.59 (0.01, 15.01)	0.60 (0.01, 9.48)	-0.02 (-0.07, 0.35)
IM TU 1000 mg/9 wk		5.34 (0.13, 307.90)	4.41 (0.14, 24.86)	0.16 (-0.05, 0.89)
IM TU 1000 mg/12 wk		0.50 (0.15, 1.63)	0.52 (0.16, 1.60)	-0.02 (-0.06, 0.02)
IM TE 100 mg/wk		0.62 (0.02, 15.75)	0.64 (0.02, 9.87)	-0.02 (-0.07, 0.36)
IM TE 125 mg/wk		7.03 (0.90, 70.40)	5.43 (0.90, 20.36)	0.21 (0.00, 0.70)
IM TE 150 mg/2 wk		0.83 (0.04, 11.99)	0.83 (0.04, 8.22)	-0.01 (-0.06, 0.30)
IM TE 200 mg/2wk		2.72 (0.68, 12.29)	2.52 (0.70, 8.76)	0.07 (-0.02, 0.29)
IM TE 250 mg/3wk		3.75 (0.44, 44.82)	3.31 (0.46, 16.46)	0.11 (-0.03, 0.62)
IM TE 250 mg/4 wk		1.70 (0.16, 20.89)	1.64 (0.16, 11.80)	0.03 (-0.05, 0.43)
IM TE 300 mg/3wk		0.79 (0.12, 5.05)	0.80 (0.12, 4.36)	-0.01 (-0.06, 0.13)
IM TE 50-400 mg/wk		0.71 (0.02, 18.47)	0.72 (0.02, 10.72)	-0.01 (-0.07, 0.41)
IM TC 200 mg/2 wk		5.13 (0.61, 58.82)	4.28 (0.63, 18.66)	0.15 (-0.02, 0.66)
Gel 1%, 100 mg/wk	Gel 1% 75 mg/d	0.22 (0.02, 2.15)	0.26 (0.05, 2.08)	-0.12 (-0.65, 0.03)
Gel 1.62% 40.5 mg/d		2.68 (0.12, 92.05)	1.99 (0.24, 19.69)	0.15 (-0.41, 0.77)
Gel 2% 60 mg/d		0.46 (0.03, 5.21)	0.51 (0.08, 4.56)	-0.07 (-0.60, 0.12)
Oral TU 120 mg/d		0.16 (0.00, 8.25)	0.20 (0.00, 5.56)	-0.11 (-0.64, 0.31)
Oral TU 160 mg/d		0.29 (0.02, 3.05)	0.33 (0.06, 2.86)	-0.11 (-0.63, 0.06)
Oral TU 120-160 mg/d		0.14 (0.00, 7.06)	0.17 (0.00, 5.02)	-0.12 (-0.64, 0.25)
IM TU 1000 mg/9 wk		1.30 (0.02, 112.70)	1.21 (0.03, 16.81)	0.03 (-0.54, 0.78)
IM TU 1000 mg/12 wk		0.12 (0.01, 1.26)	0.15 (0.02, 1.25)	-0.14 (-0.67, 0.01)
IM TE 100 mg/wk		0.14 (0.00, 7.27)	0.17 (0.00, 5.12)	-0.11 (-0.64, 0.26)
IM TE 125 mg/wk		1.73 (0.07, 38.45)	1.51 (0.15, 15.41)	0.07 (-0.49, 0.62)
IM TE 150 mg/2 wk		0.19 (0.00, 6.20)	0.23 (0.01, 4.70)	-0.11 (-0.64, 0.21)
IM TE 200 mg/2wk		0.67 (0.04, 8.76)	0.71 (0.11, 6.84)	-0.04 (-0.57, 0.22)
IM TE 250 mg/3wk		0.93 (0.04, 22.08)	0.95 (0.08, 11.17)	-0.01 (-0.56, 0.50)
IM TE 250 mg/4 wk		0.42 (0.01, 9.61)	0.48 (0.03, 6.34)	-0.07 (-0.60, 0.33)
IM TE 300 mg/3wk		0.19 (0.01, 2.87)	0.23 (0.02, 2.64)	-0.12 (-0.65, 0.07)
IM TE 50-400 mg/wk		0.17 (0.00, 7.91)	0.21 (0.00, 5.33)	-0.11 (-0.65, 0.29)
IM TC 200 mg/2 wk		1.27 (0.05, 29.57)	1.20 (0.11, 13.33)	0.03 (-0.52, 0.56)
Gel 1.62% 40.5 mg/d	Gel 1%, 100 mg/wk	12.04 (1.35, 214.50)	8.00 (1.32, 32.06)	0.30 (0.02, 0.85)
Gel 2% 60 mg/d		2.06 (0.53, 8.85)	1.97 (0.54, 7.38)	0.04 (-0.03, 0.18)
Oral TU 120 mg/d		0.78 (0.02, 21.32)	0.78 (0.02, 12.43)	-0.01 (-0.07, 0.41)
Oral TU 160 mg/d		1.27 (0.37, 5.05)	1.26 (0.38, 4.60)	0.01 (-0.05, 0.10)
Oral TU 120-160 mg/d		0.65 (0.01, 17.79)	0.66 (0.01, 11.30)	-0.01 (-0.07, 0.35)
IM TU 1000 mg/9 wk		5.99 (0.14, 341.80)	4.86 (0.15, 30.27)	0.16 (-0.05, 0.89)
IM TU 1000 mg/12 wk		0.56 (0.15, 2.10)	0.57 (0.16, 2.04)	-0.02 (-0.07, 0.02)
IM TE 100 mg/wk		0.68 (0.02, 18.28)	0.69 (0.02, 11.30)	-0.01 (-0.07, 0.37)
IM TE 125 mg/wk		7.80 (0.88, 85.90)	5.94 (0.89, 26.10)	0.21 (-0.01, 0.71)
IM TE 150 mg/2 wk		0.92 (0.04, 14.93)	0.92 (0.05, 10.24)	0.00 (-0.07, 0.31)
IM TE 200 mg/2wk		3.01 (0.68, 14.57)	2.76 (0.69, 10.68)	0.07 (-0.02, 0.29)
IM TE 250 mg/3wk		4.15 (0.44, 53.17)	3.63 (0.46, 20.50)	0.11 (-0.03, 0.62)
IM TE 250 mg/4 wk		1.89 (0.16, 24.96)	1.82 (0.17, 14.22)	0.03 (-0.05, 0.43)
IM TE 300 mg/3wk		0.86 (0.12, 6.10)	0.87 (0.12, 5.25)	-0.01 (-0.06, 0.14)
IM TE 50-400 mg/wk		0.79 (0.02, 21.47)	0.80 (0.02, 12.58)	-0.01 (-0.07, 0.41)
IM TC 200 mg/2 wk		5.64 (0.66, 68.34)	4.66 (0.67, 22.80)	0.15 (-0.02, 0.67)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.17 (0.01, 1.72)	0.25 (0.05, 1.61)	-0.25 (-0.81, 0.05)
Oral TU 120 mg/d		0.06 (0.00, 3.07)	0.10 (0.00, 2.24)	-0.28 (-0.85, 0.18)
Oral TU 160 mg/d		0.11 (0.01, 1.10)	0.16 (0.04, 1.09)	-0.29 (-0.84, 0.01)
Oral TU 120-160 mg/d		0.05 (0.00, 2.82)	0.08 (0.00, 2.19)	-0.29 (-0.85, 0.16)
IM TU 1000 mg/9 wk		0.46 (0.00, 48.30)	0.61 (0.02, 7.08)	-0.11 (-0.77, 0.70)

IM TU 1000 mg/12 wk		0.05 (0.00, 0.45)	0.07 (0.02, 0.48)	-0.32 (-0.86, -0.04)
IM TE 100 mg/wk		0.05 (0.00, 2.54)	0.09 (0.00, 1.97)	-0.29 (-0.85, 0.15)
IM TE 125 mg/wk		0.62 (0.02, 13.10)	0.74 (0.09, 5.65)	-0.08 (-0.70, 0.50)
IM TE 150 mg/2 wk		0.07 (0.00, 2.07)	0.12 (0.01, 1.74)	-0.28 (-0.84, 0.11)
IM TE 200 mg/2wk		0.25 (0.01, 2.77)	0.35 (0.07, 2.35)	-0.22 (-0.77, 0.13)
IM TE 250 mg/3wk		0.32 (0.01, 8.28)	0.46 (0.05, 4.37)	-0.17 (-0.75, 0.40)
IM TE 250 mg/4 wk		0.15 (0.00, 3.47)	0.23 (0.02, 2.60)	-0.24 (-0.81, 0.21)
IM TE 300 mg/3wk		0.07 (0.00, 1.04)	0.11 (0.01, 1.03)	-0.30 (-0.85, 0.00)
IM TE 50-400 mg/wk		0.06 (0.00, 2.82)	0.11 (0.00, 2.14)	-0.28 (-0.85, 0.17)
IM TC 200 mg/2 wk		0.46 (0.02, 9.80)	0.59 (0.07, 4.68)	-0.13 (-0.74, 0.45)
Oral TU 120 mg/d	Gel 2% 60 mg/d	0.37 (0.01, 11.56)	0.39 (0.01, 7.04)	-0.04 (-0.19, 0.37)
Oral TU 160 mg/d		0.61 (0.14, 2.90)	0.64 (0.17, 2.69)	-0.03 (-0.17, 0.07)
Oral TU 120-160 mg/d		0.30 (0.01, 9.09)	0.33 (0.01, 6.01)	-0.05 (-0.19, 0.31)
IM TU 1000 mg/9 wk		2.83 (0.06, 179.00)	2.41 (0.07, 17.56)	0.12 (-0.14, 0.85)
IM TU 1000 mg/12 wk		0.27 (0.06, 1.19)	0.29 (0.07, 1.18)	-0.06 (-0.20, 0.01)
IM TE 100 mg/wk		0.33 (0.01, 9.38)	0.35 (0.01, 6.04)	-0.05 (-0.19, 0.32)
IM TE 125 mg/wk		3.77 (0.37, 43.92)	2.99 (0.41, 14.88)	0.16 (-0.09, 0.66)
IM TE 150 mg/2 wk		0.44 (0.02, 7.65)	0.46 (0.02, 5.52)	-0.04 (-0.18, 0.27)
IM TE 200 mg/2wk		1.46 (0.26, 8.36)	1.40 (0.30, 6.34)	0.03 (-0.13, 0.25)
IM TE 250 mg/3wk		2.01 (0.19, 27.19)	1.84 (0.21, 11.45)	0.07 (-0.13, 0.58)
IM TE 250 mg/4 wk		0.91 (0.07, 13.22)	0.92 (0.08, 7.89)	-0.01 (-0.16, 0.39)
IM TE 300 mg/3wk		0.42 (0.05, 3.27)	0.44 (0.06, 2.93)	-0.04 (-0.19, 0.10)
IM TE 50-400 mg/wk		0.37 (0.01, 11.52)	0.39 (0.01, 6.94)	-0.04 (-0.19, 0.36)
IM TC 200 mg/2 wk		2.74 (0.27, 34.84)	2.36 (0.30, 13.02)	0.11 (-0.11, 0.62)
Oral TU 160 mg/d	Oral TU 120 mg/d	1.68 (0.06, 82.06)	1.64 (0.10, 75.37)	0.02 (-0.39, 0.11)
Oral TU 120-160 mg/d		0.82 (0.01, 122.60)	0.83 (0.01, 91.26)	0.00 (-0.40, 0.35)
IM TU 1000 mg/9 wk		7.63 (0.06, 2130.00)	5.37 (0.09, 397.00)	0.14 (-0.27, 0.89)
IM TU 1000 mg/12 wk		0.72 (0.02, 41.46)	0.73 (0.04, 39.99)	-0.01 (-0.43, 0.04)
IM TE 100 mg/wk		0.88 (0.01, 114.50)	0.88 (0.01, 86.98)	0.00 (-0.40, 0.35)
IM TE 125 mg/wk		10.44 (0.24, 761.50)	7.32 (0.33, 393.60)	0.19 (-0.23, 0.70)
IM TE 150 mg/2 wk		1.17 (0.01, 146.00)	1.16 (0.02, 110.80)	0.00 (-0.40, 0.31)
IM TE 200 mg/2wk		4.03 (0.12, 216.80)	3.61 (0.19, 175.60)	0.07 (-0.34, 0.29)
IM TE 250 mg/3wk		5.59 (0.13, 436.30)	4.62 (0.19, 258.10)	0.10 (-0.30, 0.61)
IM TE 250 mg/4 wk		2.46 (0.05, 224.70)	2.29 (0.07, 164.90)	0.03 (-0.36, 0.43)
IM TE 300 mg/3wk		1.11 (0.03, 78.38)	1.11 (0.04, 70.90)	0.00 (-0.41, 0.15)
IM TE 50-400 mg/wk		1.01 (0.01, 159.70)	1.01 (0.01, 112.50)	0.00 (-0.40, 0.40)
IM TC 200 mg/2 wk		7.37 (0.16, 648.90)	5.76 (0.24, 350.40)	0.14 (-0.27, 0.67)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.50 (0.01, 13.86)	0.52 (0.01, 8.97)	-0.02 (-0.11, 0.34)
IM TU 1000 mg/9 wk		4.57 (0.10, 279.50)	3.76 (0.11, 26.09)	0.15 (-0.08, 0.88)
IM TU 1000 mg/12 wk		0.44 (0.10, 1.73)	0.45 (0.11, 1.69)	-0.03 (-0.11, 0.02)
IM TE 100 mg/wk		0.54 (0.01, 14.39)	0.55 (0.01, 9.07)	-0.02 (-0.11, 0.35)
IM TE 125 mg/wk		6.07 (0.63, 68.56)	4.66 (0.65, 21.67)	0.20 (-0.03, 0.69)
IM TE 150 mg/2 wk		0.71 (0.03, 11.55)	0.72 (0.03, 8.06)	-0.01 (-0.11, 0.29)
IM TE 200 mg/2wk		2.35 (0.45, 12.54)	2.19 (0.48, 9.33)	0.06 (-0.05, 0.28)
IM TE 250 mg/3wk		3.23 (0.33, 42.24)	2.85 (0.35, 16.79)	0.10 (-0.06, 0.61)
IM TE 250 mg/4 wk		1.47 (0.12, 20.10)	1.43 (0.13, 11.53)	0.02 (-0.09, 0.42)
IM TE 300 mg/3wk		0.68 (0.08, 4.87)	0.69 (0.09, 4.28)	-0.02 (-0.10, 0.13)
IM TE 50-400 mg/wk		0.60 (0.02, 17.98)	0.62 (0.02, 10.73)	-0.02 (-0.11, 0.40)
IM TC 200 mg/2 wk		4.40 (0.46, 52.83)	3.66 (0.49, 18.74)	0.14 (-0.04, 0.65)
IM TU 1000 mg/9 wk	Oral TU 120-160 mg/d	9.97 (0.06, 2124.00)	6.67 (0.08, 455.80)	0.15 (-0.24, 0.89)

IM TU 1000 mg/12 wk		0.86 (0.03, 44.86)	0.86 (0.05, 43.51)	0.00 (-0.37, 0.04)
IM TE 100 mg/wk		1.07 (0.01, 128.50)	1.07 (0.01, 93.40)	0.00 (-0.35, 0.37)
IM TE 125 mg/wk		12.28 (0.28, 1005.00)	8.45 (0.37, 480.00)	0.20 (-0.18, 0.71)
IM TE 150 mg/2 wk		1.34 (0.02, 149.00)	1.32 (0.03, 118.20)	0.01 (-0.34, 0.31)
IM TE 200 mg/2wk		4.70 (0.16, 248.70)	4.20 (0.23, 202.90)	0.08 (-0.28, 0.30)
IM TE 250 mg/3wk		6.63 (0.15, 519.00)	5.42 (0.20, 309.80)	0.11 (-0.24, 0.62)
IM TE 250 mg/4 wk		3.07 (0.05, 292.60)	2.82 (0.07, 201.10)	0.04 (-0.31, 0.43)
IM TE 300 mg/3wk		1.38 (0.03, 88.05)	1.36 (0.05, 79.78)	0.01 (-0.35, 0.15)
IM TE 50-400 mg/wk		1.31 (0.01, 140.60)	1.29 (0.02, 97.85)	0.00 (-0.34, 0.41)
IM TC 200 mg/2 wk		9.13 (0.21, 690.90)	6.96 (0.28, 389.10)	0.15 (-0.22, 0.67)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.09 (0.00, 3.93)	0.12 (0.02, 3.84)	-0.18 (-0.91, 0.02)
IM TE 100 mg/wk		0.11 (0.00, 15.20)	0.15 (0.00, 11.62)	-0.15 (-0.89, 0.23)
IM TE 125 mg/wk		1.36 (0.01, 102.00)	1.24 (0.10, 48.65)	0.04 (-0.75, 0.62)
IM TE 150 mg/2 wk		0.15 (0.00, 14.29)	0.21 (0.01, 11.51)	-0.15 (-0.88, 0.21)
IM TE 200 mg/2wk		0.52 (0.01, 25.88)	0.58 (0.07, 21.37)	-0.08 (-0.82, 0.23)
IM TE 250 mg/3wk		0.75 (0.02, 19.79)	0.82 (0.10, 14.82)	-0.03 (-0.72, 0.34)
IM TE 250 mg/4 wk		0.33 (0.00, 23.16)	0.41 (0.02, 16.63)	-0.10 (-0.85, 0.32)
IM TE 300 mg/3wk		0.15 (0.00, 8.48)	0.19 (0.01, 7.74)	-0.16 (-0.89, 0.09)
IM TE 50-400 mg/wk		0.13 (0.00, 17.85)	0.19 (0.00, 12.81)	-0.14 (-0.89, 0.29)
IM TC 200 mg/2 wk		0.94 (0.01, 82.03)	0.96 (0.08, 42.38)	-0.01 (-0.76, 0.57)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.25 (0.03, 33.94)	1.24 (0.03, 21.19)	0.01 (-0.05, 0.39)
IM TE 125 mg/wk		13.96 (1.53, 155.40)	10.37 (1.50, 49.63)	0.23 (0.02, 0.73)
IM TE 150 mg/2 wk		1.65 (0.07, 26.87)	1.62 (0.07, 18.45)	0.01 (-0.04, 0.33)
IM TE 200 mg/2wk		5.35 (1.14, 29.79)	4.81 (1.13, 21.81)	0.09 (0.00, 0.31)
IM TE 250 mg/3wk		7.46 (0.76, 95.56)	6.37 (0.77, 37.44)	0.13 (-0.01, 0.64)
IM TE 250 mg/4 wk		3.39 (0.27, 48.37)	3.19 (0.28, 27.35)	0.05 (-0.03, 0.45)
IM TE 300 mg/3wk		1.53 (0.20, 11.83)	1.51 (0.21, 10.12)	0.01 (-0.03, 0.15)
IM TE 50-400 mg/wk		1.39 (0.04, 43.58)	1.37 (0.04, 24.87)	0.01 (-0.04, 0.43)
IM TC 200 mg/2 wk		10.17 (1.09, 118.90)	8.18 (1.09, 43.22)	0.17 (0.00, 0.68)
IM TE 125 mg/wk	IM TE 100 mg/wk	12.11 (0.25, 700.80)	8.30 (0.35, 350.30)	0.20 (-0.20, 0.71)
IM TE 150 mg/2 wk		1.31 (0.02, 102.10)	1.29 (0.03, 81.20)	0.01 (-0.36, 0.30)
IM TE 200 mg/2wk		4.42 (0.14, 212.20)	3.93 (0.22, 169.60)	0.07 (-0.30, 0.30)
IM TE 250 mg/3wk		6.48 (0.13, 403.60)	5.24 (0.19, 228.30)	0.11 (-0.27, 0.61)
IM TE 250 mg/4 wk		2.95 (0.05, 173.50)	2.72 (0.08, 125.40)	0.04 (-0.33, 0.43)
IM TE 300 mg/3wk		1.27 (0.03, 67.34)	1.26 (0.05, 60.89)	0.01 (-0.37, 0.15)
IM TE 50-400 mg/wk		1.12 (0.01, 151.40)	1.11 (0.01, 103.80)	0.00 (-0.35, 0.40)
IM TC 200 mg/2 wk		8.45 (0.20, 551.20)	6.45 (0.28, 276.70)	0.14 (-0.22, 0.66)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.11 (0.00, 3.07)	0.16 (0.01, 2.50)	-0.20 (-0.70, 0.14)
IM TE 200 mg/2wk		0.38 (0.03, 4.28)	0.46 (0.09, 3.48)	-0.13 (-0.63, 0.17)
IM TE 250 mg/3wk		0.53 (0.03, 12.61)	0.62 (0.06, 6.32)	-0.09 (-0.61, 0.45)
IM TE 250 mg/4 wk		0.24 (0.01, 5.67)	0.31 (0.02, 3.96)	-0.15 (-0.67, 0.27)
IM TE 300 mg/3wk		0.11 (0.01, 1.55)	0.15 (0.02, 1.49)	-0.21 (-0.70, 0.03)
IM TE 50-400 mg/wk		0.10 (0.00, 4.20)	0.14 (0.00, 3.01)	-0.19 (-0.70, 0.23)
IM TC 200 mg/2 wk		0.71 (0.04, 14.33)	0.78 (0.09, 6.87)	-0.05 (-0.58, 0.49)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.30 (0.18, 86.63)	2.99 (0.24, 67.99)	0.07 (-0.24, 0.30)
IM TE 250 mg/3wk		4.82 (0.16, 184.20)	4.03 (0.21, 102.80)	0.10 (-0.20, 0.60)
IM TE 250 mg/4 wk		2.16 (0.06, 89.66)	2.03 (0.08, 60.97)	0.03 (-0.27, 0.43)
IM TE 300 mg/3wk		0.95 (0.04, 29.52)	0.95 (0.05, 26.38)	0.00 (-0.31, 0.14)
IM TE 50-400 mg/wk		0.87 (0.01, 61.14)	0.88 (0.01, 41.40)	0.00 (-0.30, 0.40)

IM TC 200 mg/2 wk		6.37 (0.22, 248.10)	5.06 (0.28, 120.20)	0.14 (-0.19, 0.66)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.37 (0.11, 20.90)	1.30 (0.14, 8.90)	0.03 (-0.22, 0.55)
IM TE 250 mg/4 wk		0.61 (0.04, 10.10)	0.65 (0.05, 6.24)	-0.04 (-0.27, 0.37)
IM TE 300 mg/3wk		0.28 (0.03, 2.51)	0.31 (0.04, 2.28)	-0.07 (-0.29, 0.08)
IM TE 50-400 mg/wk		0.26 (0.01, 8.14)	0.28 (0.01, 5.18)	-0.07 (-0.29, 0.34)
IM TC 200 mg/2 wk		1.86 (0.16, 25.94)	1.67 (0.21, 10.11)	0.07 (-0.20, 0.60)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.44 (0.02, 10.79)	0.50 (0.04, 7.11)	-0.07 (-0.55, 0.34)
IM TE 300 mg/3wk		0.20 (0.01, 3.27)	0.24 (0.02, 2.97)	-0.11 (-0.62, 0.08)
IM TE 50-400 mg/wk		0.19 (0.00, 9.37)	0.23 (0.00, 6.26)	-0.10 (-0.61, 0.32)
IM TC 200 mg/2 wk		1.36 (0.06, 30.52)	1.27 (0.12, 13.36)	0.04 (-0.48, 0.58)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.45 (0.02, 8.41)	0.48 (0.04, 7.55)	-0.03 (-0.43, 0.12)
IM TE 50-400 mg/wk		0.40 (0.01, 24.86)	0.43 (0.01, 16.60)	-0.03 (-0.42, 0.37)
IM TC 200 mg/2 wk		3.07 (0.12, 82.13)	2.55 (0.18, 36.58)	0.10 (-0.32, 0.63)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.90 (0.02, 37.63)	0.91 (0.02, 23.61)	0.00 (-0.14, 0.41)
IM TC 200 mg/2 wk		6.65 (0.47, 117.40)	5.30 (0.50, 50.45)	0.15 (-0.06, 0.67)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	7.58 (0.15, 503.50)	5.84 (0.22, 276.80)	0.14 (-0.29, 0.66)

Withdrawals due to adverse events, continuity correction, treatments with zero events dropped — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	2.45 (0.79, 7.31)	2.26 (0.80, 5.44)	0.07 (-0.01, 0.24)
Gel 1% 5 mg/d		0.83 (0.31, 2.32)	0.84 (0.33, 2.16)	-0.01 (-0.04, 0.06)
Gel 1% 50 mg/d		0.87 (0.46, 1.61)	0.88 (0.47, 1.56)	-0.01 (-0.03, 0.03)
Gel 1% 75 mg/d		3.60 (0.45, 39.26)	3.12 (0.46, 12.79)	0.12 (-0.03, 0.64)
Gel 1%, 100 mg/wk		0.80 (0.33, 1.81)	0.81 (0.34, 1.73)	-0.01 (-0.04, 0.04)
Gel 1.62% 40.5 mg/d		9.31 (1.26, 178.00)	6.28 (1.24, 17.61)	0.31 (0.01, 0.85)
Gel 2% 60 mg/d		1.62 (0.53, 5.08)	1.57 (0.55, 4.13)	0.03 (-0.03, 0.18)
Oral TU 160 mg/d		1.02 (0.38, 2.89)	1.02 (0.40, 2.61)	0.00 (-0.04, 0.09)
IM TU 1000 mg/12 wk		0.43 (0.16, 1.17)	0.45 (0.16, 1.16)	-0.03 (-0.05, 0.01)
IM TE 125 mg/wk		5.96 (0.79, 62.05)	4.62 (0.80, 14.39)	0.21 (-0.01, 0.73)
IM TE 150 mg/2 wk		0.73 (0.04, 11.04)	0.75 (0.04, 7.10)	-0.01 (-0.06, 0.34)
IM TE 200 mg/2wk		2.38 (0.66, 9.73)	2.20 (0.68, 6.67)	0.07 (-0.02, 0.30)
IM TE 250 mg/3wk		4.07 (0.47, 60.27)	3.45 (0.49, 14.33)	0.14 (-0.03, 0.72)
IM TE 250 mg/4 wk		1.57 (0.15, 20.46)	1.52 (0.16, 9.95)	0.03 (-0.05, 0.49)
IM TE 300 mg/3wk		0.68 (0.10, 3.94)	0.69 (0.11, 3.37)	-0.02 (-0.06, 0.13)
IM TC 200 mg/2 wk		4.28 (0.59, 49.63)	3.60 (0.61, 13.60)	0.15 (-0.02, 0.69)
Gel 1% 5 mg/d	Patch 5 mg/d	0.34 (0.08, 1.60)	0.37 (0.10, 1.54)	-0.08 (-0.25, 0.03)
Gel 1% 50 mg/d		0.36 (0.11, 1.15)	0.39 (0.15, 1.14)	-0.08 (-0.25, 0.01)
Gel 1% 75 mg/d		1.50 (0.14, 20.53)	1.40 (0.17, 7.92)	0.05 (-0.19, 0.57)
Gel 1%, 100 mg/wk		0.33 (0.10, 1.10)	0.36 (0.12, 1.09)	-0.08 (-0.25, 0.01)
Gel 1.62% 40.5 mg/d		3.92 (0.38, 87.27)	2.76 (0.44, 12.44)	0.23 (-0.12, 0.79)
Gel 2% 60 mg/d		0.66 (0.15, 3.39)	0.69 (0.18, 2.90)	-0.04 (-0.21, 0.13)
Oral TU 160 mg/d		0.42 (0.10, 1.99)	0.45 (0.12, 1.86)	-0.07 (-0.25, 0.06)
IM TU 1000 mg/12 wk		0.18 (0.04, 0.80)	0.20 (0.05, 0.81)	-0.10 (-0.28, -0.01)
IM TE 125 mg/wk		2.43 (0.25, 33.75)	2.01 (0.29, 9.87)	0.13 (-0.16, 0.67)
IM TE 150 mg/2 wk		0.30 (0.01, 5.43)	0.33 (0.02, 3.75)	-0.08 (-0.26, 0.26)
IM TE 200 mg/2wk		0.97 (0.22, 4.85)	0.98 (0.27, 3.75)	0.00 (-0.18, 0.22)
IM TE 250 mg/3wk		1.70 (0.14, 30.02)	1.55 (0.17, 8.82)	0.07 (-0.19, 0.65)

IM TE 250 mg/4 wk		0.65 (0.05, 10.52)	0.68 (0.06, 5.58)	-0.04 (-0.23, 0.42)
IM TE 300 mg/3wk		0.28 (0.03, 2.26)	0.31 (0.04, 2.05)	-0.08 (-0.26, 0.08)
IM TC 200 mg/2 wk		1.79 (0.19, 25.38)	1.61 (0.22, 8.43)	0.08 (-0.17, 0.62)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.05 (0.31, 3.22)	1.05 (0.33, 3.07)	0.00 (-0.08, 0.05)
Gel 1% 75 mg/d		4.37 (0.43, 53.10)	3.71 (0.45, 19.93)	0.13 (-0.04, 0.64)
Gel 1%, 100 mg/wk		0.96 (0.24, 3.41)	0.96 (0.26, 3.22)	0.00 (-0.08, 0.06)
Gel 1.62% 40.5 mg/d		11.37 (1.16, 248.80)	7.32 (1.14, 31.17)	0.31 (0.01, 0.86)
Gel 2% 60 mg/d		1.97 (0.43, 8.62)	1.87 (0.45, 7.14)	0.04 (-0.05, 0.19)
Oral TU 160 mg/d		1.23 (0.31, 5.09)	1.21 (0.33, 4.60)	0.01 (-0.07, 0.10)
IM TU 1000 mg/12 wk		0.52 (0.12, 2.08)	0.53 (0.14, 2.02)	-0.02 (-0.10, 0.03)
IM TE 125 mg/wk		7.22 (0.75, 88.54)	5.41 (0.77, 24.52)	0.21 (-0.02, 0.73)
IM TE 150 mg/2 wk		0.87 (0.04, 15.56)	0.88 (0.04, 10.10)	-0.01 (-0.09, 0.34)
IM TE 200 mg/2wk		2.88 (0.56, 15.29)	2.62 (0.58, 10.94)	0.08 (-0.04, 0.31)
IM TE 250 mg/3wk		4.95 (0.44, 89.63)	4.09 (0.46, 23.97)	0.15 (-0.04, 0.73)
IM TE 250 mg/4 wk		1.89 (0.15, 28.44)	1.80 (0.16, 14.71)	0.04 (-0.07, 0.49)
IM TE 300 mg/3wk		0.81 (0.10, 5.99)	0.81 (0.10, 5.13)	-0.01 (-0.09, 0.14)
IM TC 200 mg/2 wk		5.17 (0.57, 69.47)	4.23 (0.59, 22.36)	0.15 (-0.03, 0.69)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	4.14 (0.47, 48.50)	3.55 (0.48, 16.49)	0.13 (-0.03, 0.65)
Gel 1%, 100 mg/wk		0.91 (0.34, 2.44)	0.91 (0.36, 2.31)	0.00 (-0.05, 0.05)
Gel 1.62% 40.5 mg/d		10.70 (1.35, 219.60)	7.06 (1.32, 24.22)	0.31 (0.02, 0.86)
Gel 2% 60 mg/d		1.87 (0.52, 7.02)	1.79 (0.54, 5.70)	0.04 (-0.03, 0.19)
Oral TU 160 mg/d		1.17 (0.37, 4.11)	1.16 (0.38, 3.68)	0.01 (-0.05, 0.10)
IM TU 1000 mg/12 wk		0.50 (0.15, 1.62)	0.51 (0.16, 1.58)	-0.02 (-0.07, 0.02)
IM TE 125 mg/wk		6.86 (0.83, 77.16)	5.25 (0.84, 19.16)	0.21 (-0.01, 0.73)
IM TE 150 mg/2 wk		0.84 (0.04, 13.73)	0.85 (0.04, 8.85)	-0.01 (-0.07, 0.34)
IM TE 200 mg/2wk		2.74 (0.68, 12.47)	2.51 (0.70, 8.77)	0.08 (-0.02, 0.31)
IM TE 250 mg/3wk		4.71 (0.50, 74.22)	3.93 (0.51, 18.54)	0.15 (-0.03, 0.73)
IM TE 250 mg/4 wk		1.78 (0.17, 25.43)	1.71 (0.18, 12.76)	0.04 (-0.05, 0.49)
IM TE 300 mg/3wk		0.77 (0.11, 5.07)	0.78 (0.11, 4.32)	-0.01 (-0.06, 0.14)
IM TC 200 mg/2 wk		4.96 (0.63, 60.52)	4.10 (0.64, 17.44)	0.16 (-0.02, 0.69)
Gel 1%, 100 mg/wk	Gel 1% 75 mg/d	0.22 (0.02, 2.08)	0.26 (0.05, 2.01)	-0.13 (-0.65, 0.03)
Gel 1.62% 40.5 mg/d		2.68 (0.12, 89.97)	1.93 (0.24, 16.87)	0.16 (-0.40, 0.77)
Gel 2% 60 mg/d		0.45 (0.03, 5.09)	0.50 (0.09, 4.40)	-0.08 (-0.60, 0.13)
Oral TU 160 mg/d		0.28 (0.02, 2.91)	0.33 (0.06, 2.72)	-0.12 (-0.63, 0.06)
IM TU 1000 mg/12 wk		0.12 (0.01, 1.21)	0.14 (0.03, 1.20)	-0.15 (-0.67, 0.01)
IM TE 125 mg/wk		1.65 (0.08, 39.04)	1.44 (0.16, 14.17)	0.07 (-0.48, 0.63)
IM TE 150 mg/2 wk		0.20 (0.00, 6.22)	0.24 (0.01, 4.54)	-0.12 (-0.64, 0.24)
IM TE 200 mg/2wk		0.66 (0.04, 8.08)	0.71 (0.11, 6.22)	-0.05 (-0.58, 0.24)
IM TE 250 mg/3wk		1.15 (0.04, 33.64)	1.11 (0.10, 12.20)	0.02 (-0.53, 0.62)
IM TE 250 mg/4 wk		0.43 (0.02, 11.15)	0.50 (0.03, 6.84)	-0.08 (-0.60, 0.37)
IM TE 300 mg/3wk		0.18 (0.01, 2.84)	0.22 (0.02, 2.58)	-0.13 (-0.65, 0.08)
IM TC 200 mg/2 wk		1.21 (0.05, 28.54)	1.15 (0.12, 11.93)	0.02 (-0.52, 0.58)
Gel 1.62% 40.5 mg/d	Gel 1%, 100 mg/wk	11.93 (1.31, 242.20)	7.69 (1.28, 30.38)	0.32 (0.02, 0.86)
Gel 2% 60 mg/d		2.05 (0.52, 8.87)	1.95 (0.54, 7.24)	0.04 (-0.03, 0.19)
Oral TU 160 mg/d		1.28 (0.36, 5.22)	1.26 (0.38, 4.68)	0.01 (-0.05, 0.11)
IM TU 1000 mg/12 wk		0.54 (0.15, 2.10)	0.55 (0.16, 2.04)	-0.02 (-0.08, 0.03)
IM TE 125 mg/wk		7.48 (0.85, 92.34)	5.64 (0.86, 24.50)	0.22 (-0.01, 0.74)
IM TE 150 mg/2 wk		0.93 (0.04, 15.61)	0.94 (0.05, 9.99)	0.00 (-0.07, 0.34)
IM TE 200 mg/2wk		3.01 (0.67, 14.99)	2.74 (0.69, 10.64)	0.08 (-0.02, 0.31)
IM TE 250 mg/3wk		5.21 (0.49, 87.36)	4.30 (0.51, 23.10)	0.15 (-0.03, 0.73)

IM TE 250 mg/4 wk		2.00 (0.17, 28.89)	1.90 (0.18, 14.40)	0.04 (-0.06, 0.50)
IM TE 300 mg/3wk		0.85 (0.11, 6.13)	0.86 (0.12, 5.23)	-0.01 (-0.07, 0.15)
IM TC 200 mg/2 wk		5.47 (0.64, 71.24)	4.48 (0.65, 21.88)	0.16 (-0.02, 0.70)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.17 (0.01, 1.80)	0.25 (0.06, 1.67)	-0.27 (-0.82, 0.06)
Oral TU 160 mg/d		0.11 (0.01, 1.08)	0.17 (0.04, 1.07)	-0.30 (-0.85, 0.01)
IM TU 1000 mg/12 wk		0.04 (0.00, 0.46)	0.07 (0.02, 0.49)	-0.34 (-0.88, -0.04)
IM TE 125 mg/wk		0.61 (0.02, 14.21)	0.73 (0.10, 5.40)	-0.09 (-0.71, 0.53)
IM TE 150 mg/2 wk		0.07 (0.00, 2.40)	0.13 (0.01, 1.98)	-0.29 (-0.86, 0.13)
IM TE 200 mg/2wk		0.25 (0.01, 2.95)	0.36 (0.07, 2.43)	-0.22 (-0.79, 0.14)
IM TE 250 mg/3wk		0.44 (0.01, 11.97)	0.58 (0.06, 4.96)	-0.14 (-0.76, 0.49)
IM TE 250 mg/4 wk		0.16 (0.00, 4.16)	0.25 (0.02, 2.83)	-0.25 (-0.83, 0.25)
IM TE 300 mg/3wk		0.07 (0.00, 1.04)	0.11 (0.01, 1.04)	-0.31 (-0.87, 0.00)
IM TC 200 mg/2 wk		0.44 (0.01, 11.78)	0.58 (0.07, 5.05)	-0.14 (-0.75, 0.49)
Oral TU 160 mg/d	Gel 2% 60 mg/d	0.63 (0.14, 2.94)	0.65 (0.17, 2.71)	-0.03 (-0.18, 0.07)
IM TU 1000 mg/12 wk		0.27 (0.06, 1.16)	0.29 (0.07, 1.15)	-0.06 (-0.21, 0.01)
IM TE 125 mg/wk		3.65 (0.37, 50.10)	2.86 (0.41, 14.31)	0.17 (-0.09, 0.69)
IM TE 150 mg/2 wk		0.45 (0.02, 8.54)	0.47 (0.02, 5.81)	-0.04 (-0.20, 0.30)
IM TE 200 mg/2wk		1.47 (0.25, 8.77)	1.41 (0.29, 6.44)	0.03 (-0.14, 0.27)
IM TE 250 mg/3wk		2.53 (0.22, 45.79)	2.20 (0.25, 13.32)	0.10 (-0.12, 0.68)
IM TE 250 mg/4 wk		0.96 (0.07, 15.99)	0.96 (0.08, 8.41)	0.00 (-0.18, 0.45)
IM TE 300 mg/3wk		0.41 (0.05, 3.38)	0.44 (0.05, 3.00)	-0.05 (-0.20, 0.11)
IM TC 200 mg/2 wk		2.66 (0.26, 38.71)	2.29 (0.29, 12.54)	0.11 (-0.12, 0.66)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.42 (0.10, 1.66)	0.44 (0.11, 1.63)	-0.03 (-0.12, 0.02)
IM TE 125 mg/wk		5.87 (0.62, 72.39)	4.47 (0.65, 20.03)	0.20 (-0.03, 0.72)
IM TE 150 mg/2 wk		0.71 (0.03, 12.90)	0.73 (0.03, 8.42)	-0.01 (-0.12, 0.33)
IM TE 200 mg/2wk		2.37 (0.44, 12.74)	2.19 (0.47, 9.19)	0.07 (-0.06, 0.30)
IM TE 250 mg/3wk		4.03 (0.36, 66.58)	3.37 (0.38, 19.27)	0.14 (-0.06, 0.71)
IM TE 250 mg/4 wk		1.54 (0.12, 23.72)	1.49 (0.13, 12.25)	0.03 (-0.09, 0.48)
IM TE 300 mg/3wk		0.67 (0.07, 4.97)	0.68 (0.08, 4.29)	-0.02 (-0.12, 0.13)
IM TC 200 mg/2 wk		4.24 (0.45, 58.34)	3.51 (0.48, 18.40)	0.14 (-0.05, 0.68)
IM TE 125 mg/wk	IM TU 1000 mg/12 wk	13.85 (1.49, 175.80)	10.15 (1.46, 47.99)	0.24 (0.02, 0.76)
IM TE 150 mg/2 wk		1.70 (0.08, 30.34)	1.67 (0.08, 19.68)	0.02 (-0.04, 0.36)
IM TE 200 mg/2wk		5.53 (1.13, 30.54)	4.93 (1.12, 21.56)	0.10 (0.00, 0.33)
IM TE 250 mg/3wk		9.41 (0.88, 175.80)	7.59 (0.89, 48.33)	0.17 (0.00, 0.75)
IM TE 250 mg/4 wk		3.67 (0.29, 54.69)	3.41 (0.30, 28.20)	0.06 (-0.03, 0.52)
IM TE 300 mg/3wk		1.58 (0.19, 11.91)	1.56 (0.19, 10.07)	0.01 (-0.04, 0.17)
IM TC 200 mg/2 wk		9.98 (1.08, 139.70)	7.98 (1.08, 44.34)	0.18 (0.00, 0.71)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.12 (0.00, 3.33)	0.16 (0.01, 2.61)	-0.20 (-0.72, 0.17)
IM TE 200 mg/2wk		0.40 (0.03, 4.48)	0.49 (0.09, 3.57)	-0.13 (-0.67, 0.18)
IM TE 250 mg/3wk		0.68 (0.03, 22.04)	0.76 (0.08, 8.08)	-0.06 (-0.63, 0.57)
IM TE 250 mg/4 wk		0.26 (0.01, 6.42)	0.34 (0.03, 4.03)	-0.16 (-0.70, 0.32)
IM TE 300 mg/3wk		0.11 (0.01, 1.68)	0.15 (0.02, 1.58)	-0.22 (-0.74, 0.04)
IM TC 200 mg/2 wk		0.73 (0.03, 17.95)	0.80 (0.09, 7.38)	-0.05 (-0.63, 0.54)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.25 (0.17, 85.05)	2.91 (0.24, 66.35)	0.07 (-0.26, 0.30)
IM TE 250 mg/3wk		5.83 (0.18, 293.90)	4.55 (0.23, 119.10)	0.13 (-0.22, 0.73)
IM TE 250 mg/4 wk		2.19 (0.06, 98.17)	2.04 (0.08, 64.63)	0.03 (-0.30, 0.48)
IM TE 300 mg/3wk		0.92 (0.04, 29.16)	0.92 (0.05, 25.63)	0.00 (-0.34, 0.15)
IM TC 200 mg/2 wk		6.07 (0.21, 269.50)	4.67 (0.29, 120.70)	0.14 (-0.21, 0.69)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.73 (0.13, 33.29)	1.56 (0.17, 9.92)	0.07 (-0.23, 0.66)
IM TE 250 mg/4 wk		0.66 (0.05, 10.99)	0.69 (0.06, 6.00)	-0.03 (-0.28, 0.42)

IM TE 300 mg/3wk		0.28 (0.03, 2.53)	0.31 (0.04, 2.27)	-0.08 (-0.31, 0.09)
IM TC 200 mg/2 wk		1.83 (0.16, 27.09)	1.64 (0.20, 9.48)	0.08 (-0.22, 0.62)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.37 (0.01, 10.73)	0.44 (0.03, 6.68)	-0.09 (-0.68, 0.36)
IM TE 300 mg/3wk		0.16 (0.01, 2.64)	0.20 (0.02, 2.43)	-0.15 (-0.73, 0.07)
IM TC 200 mg/2 wk		1.06 (0.04, 28.28)	1.04 (0.10, 11.62)	0.01 (-0.60, 0.58)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.43 (0.02, 7.93)	0.46 (0.03, 7.03)	-0.04 (-0.49, 0.12)
IM TC 200 mg/2 wk		2.80 (0.11, 71.27)	2.33 (0.18, 30.17)	0.10 (-0.35, 0.64)
IM TC 200 mg/2 wk	IM TE 300 mg/3wk	6.53 (0.44, 127.90)	5.18 (0.48, 50.30)	0.16 (-0.06, 0.69)

Subgroups: by route of administration

Cardiovascular death, by route, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Topical	Placebo	1.34 (0.34, 4.90)	1.34 (0.34, 4.79)	0.00 (-0.01, 0.02)
IM		0.34 (0.05, 1.91)	0.35 (0.05, 1.90)	0.00 (-0.01, 0.00)
Oral		0.12 (0.00, 4.22)	0.12 (0.00, 4.13)	-0.01 (-0.01, 0.02)
IM	Topical	0.26 (0.02, 2.19)	0.26 (0.02, 2.18)	-0.01 (-0.03, 0.01)
Oral		0.09 (0.00, 4.24)	0.09 (0.00, 4.14)	-0.01 (-0.03, 0.02)
Oral	IM	0.33 (0.00, 22.66)	0.33 (0.00, 22.07)	0.00 (-0.01, 0.02)

Cardiovascular death, by route, adjusted continuity correction — odds ratios, relative risks, and risk difference for all treatment comparisons (random-effects model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Topical	Placebo	1.30 (0.43, 3.99)	1.30 (0.43, 3.86)	0.00 (0.01, 0.03)
IM		0.61 (0.15, 2.08)	0.61 (0.16, 2.05)	-0.01 (-0.02, 0.01)
Oral		0.50 (0.03, 4.81)	0.51 (0.03, 4.58)	-0.01 (-0.02, 0.05)
IM	Topical	0.46 (0.08, 2.55)	0.47 (0.08, 2.51)	-0.01 (-0.04, 0.01)
Oral		0.39 (0.02, 4.92)	0.39 (0.02, 4.69)	-0.01 (-0.04, 0.05)
Oral	IM	0.82 (0.04, 11.82)	0.82 (0.04, 11.18)	0.00 (-0.02, 0.06)

Myocardial infarction, by route, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Topical	Placebo	0.43 (0.06, 2.13)	0.43 (0.06, 2.10)	-0.01 (-0.02, 0.01)
IM		0.19 (0.02, 1.01)	0.19 (0.02, 1.01)	-0.01 (-0.02, 0.00)
Oral		0.05 (0.00, 1.31)	0.05 (0.00, 1.30)	-0.01 (-0.02, 0.00)
IM	Topical	0.45 (0.03, 5.41)	0.45 (0.03, 5.37)	0.00 (-0.02, 0.01)
Oral		0.12 (0.00, 5.86)	0.12 (0.00, 5.78)	0.00 (-0.02, 0.01)
Oral	IM	0.27 (0.00, 14.14)	0.27 (0.00, 13.93)	0.00 (-0.01, 0.01)

Myocardial infarction, by route, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Topical	Placebo	0.65 (0.18, 2.25)	0.66 (0.19, 2.21)	-0.01 (-0.03, 0.02)
IM		0.32 (0.07, 1.28)	0.33 (0.07, 1.27)	-0.01 (-0.03, 0.00)
Oral		0.22 (0.01, 2.89)	0.22 (0.01, 2.78)	-0.02 (-0.03, 0.04)
IM	Topical	0.49 (0.08, 3.24)	0.50 (0.08, 3.19)	-0.01 (-0.03, 0.01)
Oral		0.33 (0.01, 6.11)	0.34 (0.01, 5.81)	-0.01 (-0.04, 0.05)
Oral	IM	0.66 (0.02, 13.39)	0.66 (0.02, 12.69)	0.00 (-0.02, 0.05)

Prostate cancer, by route, base case (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	0.59 (0.14, 2.17)	0.59 (0.14, 2.14)	-0.01 (-0.02, 0.01)
IM		0.57 (0.16, 1.89)	0.57 (0.16, 1.87)	-0.01 (-0.02, 0.01)
Oral		0.06 (0.00, 1.58)	0.07 (0.00, 1.57)	-0.01 (-0.02, 0.01)
IM	topical	0.97 (0.19, 4.80)	0.97 (0.20, 4.74)	0.00 (-0.02, 0.02)
Oral		0.11 (0.00, 3.93)	0.11 (0.00, 3.87)	-0.01 (-0.02, 0.01)
Oral	IM	0.11 (0.00, 3.70)	0.11 (0.00, 3.65)	-0.01 (-0.02, 0.01)

Prostate cancer, by route, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	0.70 (0.20, 2.32)	0.70 (0.21, 2.27)	-0.01 (-0.02, 0.02)
IM		0.65 (0.21, 2.05)	0.66 (0.21, 2.01)	-0.01 (-0.02, 0.02)
Oral		0.17 (0.01, 1.86)	0.17 (0.01, 1.83)	-0.02 (-0.03, 0.02)
IM	topical	0.95 (0.22, 4.02)	0.95 (0.22, 3.93)	0.00 (-0.03, 0.02)
Oral		0.23 (0.01, 3.72)	0.23 (0.01, 3.62)	-0.01 (-0.04, 0.02)
Oral	IM	0.25 (0.01, 3.72)	0.25 (0.01, 3.64)	-0.01 (-0.03, 0.02)

Serious adverse events, by route (no continuity correction) — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	1.15 (0.61, 2.14)	1.14 (0.62, 2.07)	0.00 (-0.02, 0.03)
IM		0.60 (0.19, 1.64)	0.61 (0.20, 1.61)	-0.01 (-0.04, 0.02)
Oral		0.43 (0.11, 1.58)	0.44 (0.12, 1.54)	-0.02 (-0.04, 0.02)
IM	topical	0.52 (0.15, 1.58)	0.53 (0.16, 1.55)	-0.02 (-0.05, 0.02)
Oral		0.38 (0.09, 1.64)	0.39 (0.09, 1.60)	-0.02 (-0.06, 0.02)
Oral	IM	0.73 (0.13, 4.02)	0.74 (0.14, 3.88)	-0.01 (-0.04, 0.04)

Serious adverse events, by route, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	1.16 (0.62, 2.12)	1.15 (0.63, 2.03)	0.01 (-0.02, 0.04)
IM		0.63 (0.20, 1.73)	0.64 (0.20, 1.68)	-0.02 (-0.04, 0.03)
Oral		0.45 (0.12, 1.54)	0.46 (0.12, 1.51)	-0.02 (-0.05, 0.02)
IM	topical	0.54 (0.16, 1.63)	0.56 (0.17, 1.59)	-0.02 (-0.06, 0.02)
Oral		0.38 (0.09, 1.56)	0.40 (0.09, 1.53)	-0.03 (-0.07, 0.02)
Oral	IM	0.72 (0.13, 3.78)	0.73 (0.14, 3.62)	-0.01 (-0.05, 0.04)

Withdrawals due to adverse events, by route, no continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	1.13 (0.72, 1.78)	1.13 (0.73, 1.73)	0.00 (-0.01, 0.03)
IM		1.14 (0.60, 2.10)	1.13 (0.61, 2.03)	0.01 (-0.02, 0.04)
Oral		0.86 (0.28, 2.59)	0.87 (0.29, 2.45)	0.00 (-0.03, 0.05)
IM	topical	1.01 (0.47, 2.13)	1.01 (0.48, 2.06)	0.00 (-0.03, 0.03)
Oral		0.77 (0.23, 2.47)	0.77 (0.24, 2.34)	-0.01 (-0.04, 0.05)
Oral	IM	0.76 (0.22, 2.67)	0.77 (0.23, 2.53)	-0.01 (-0.05, 0.05)

Withdrawals due to adverse events, by route, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
topical	Placebo	1.13 (0.77, 1.71)	1.13 (0.78, 1.64)	0.01 (-0.01, 0.04)
IM		1.18 (0.67, 2.07)	1.17 (0.68, 1.96)	0.01 (-0.02, 0.05)
Oral		0.96 (0.39, 2.32)	0.96 (0.41, 2.17)	0.00 (-0.04, 0.06)
IM	topical	1.04 (0.52, 2.03)	1.04 (0.55, 1.93)	0.00 (-0.04, 0.05)
Oral		0.84 (0.32, 2.22)	0.85 (0.33, 2.08)	-0.01 (-0.05, 0.06)
Oral	IM	0.82 (0.28, 2.35)	0.83 (0.30, 2.20)	-0.01 (-0.06, 0.06)

Subgroups: by treatment duration

Cardiovascular death, treatment duration 6 months or longer, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 1% 50 mg/d	Placebo	1.45(0.23,10.50)	1.45(0.23,9.71)	0.00(-0.01,0.08)
1% gel, 100 mg/d		1.49(0.11,23.29)	1.48(0.11,19.17)	0.01(-0.01,0.18)
1.62% gel, 40.5 mg/d		0.35(0.01,10.86)	0.35(0.01,9.99)	-0.01(-0.02,0.08)
2% gel, 60 mg/d		0.25(0.01,3.50)	0.25(0.01,3.41)	-0.01(-0.02,0.02)
Oral TU 120 or 160 mg/d		0.50(0.01,10.76)	0.51(0.01,9.82)	0.00(-0.02,0.09)
IM TU 1000 mg/12 wk		0.69(0.14,3.19)	0.69(0.14,3.13)	0.00(-0.01,0.02)

IM TE 200 mg/2wk		0.58(0.01,15.04)	0.58(0.01,13.29)	0.00(-0.02,0.12)
IM TE 250 mg/3 wk		0.43(0.01,12.92)	0.43(0.01,11.43)	-0.01(-0.02,0.11)
1% gel, 100 mg/d	Gel 1% 50 mg/d	1.01(0.04,29.96)	1.01(0.04,25.01)	0.00(-0.08,0.18)
1.62% gel, 40.5 mg/d		0.24(0.01,11.70)	0.24(0.01,10.77)	-0.01(-0.09,0.07)
2% gel, 60 mg/d		0.16(0.00,4.73)	0.17(0.00,4.60)	-0.01(-0.09,0.02)
Oral TU 120 or 160 mg/d		0.34(0.01,12.25)	0.35(0.01,11.22)	-0.01(-0.08,0.08)
IM TU 1000 mg/12 wk		0.47(0.04,5.20)	0.48(0.04,5.12)	-0.01(-0.08,0.02)
IM TE 200 mg/2wk		0.39(0.01,16.71)	0.39(0.01,14.85)	-0.01(-0.08,0.11)
IM TE 250 mg/3 wk		0.29(0.00,14.26)	0.29(0.00,12.54)	-0.01(-0.08,0.10)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.25(0.00,16.16)	0.25(0.00,14.80)	-0.01(-0.18,0.07)
2% gel, 60 mg/d		0.16(0.00,8.09)	0.16(0.00,7.92)	-0.01(-0.19,0.02)
Oral TU 120 or 160 mg/d		0.33(0.00,18.92)	0.33(0.00,17.38)	-0.01(-0.18,0.08)
IM TU 1000 mg/12 wk		0.47(0.02,9.58)	0.47(0.02,9.42)	-0.01(-0.18,0.02)
IM TE 200 mg/2wk		0.38(0.00,22.36)	0.39(0.00,20.24)	-0.01(-0.18,0.10)
IM TE 250 mg/3 wk		0.28(0.00,21.56)	0.28(0.00,19.24)	-0.01(-0.18,0.10)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	0.67(0.01,41.61)	0.67(0.01,40.62)	0.00(-0.08,0.03)
Oral TU 120 or 160 mg/d		1.40(0.01,146.80)	1.40(0.01,136.10)	0.00(-0.08,0.09)
IM TU 1000 mg/12 wk		1.98(0.04,71.50)	1.97(0.05,70.01)	0.00(-0.08,0.03)
IM TE 200 mg/2wk		1.54(0.01,178.30)	1.53(0.01,160.70)	0.00(-0.08,0.12)
IM TE 250 mg/3 wk		1.22(0.01,128.50)	1.22(0.01,116.20)	0.00(-0.08,0.12)
Oral TU 120 or 160 mg/d	2% gel, 60 mg/d	2.22(0.02,178.90)	2.20(0.02,166.30)	0.00(-0.03,0.09)
IM TU 1000 mg/12 wk		2.87(0.12,126.00)	2.85(0.13,123.90)	0.00(-0.03,0.03)
IM TE 200 mg/2wk		2.36(0.02,298.70)	2.34(0.02,269.10)	0.00(-0.03,0.12)
IM TE 250 mg/3 wk		1.81(0.02,222.90)	1.80(0.02,201.20)	0.00(-0.03,0.12)
IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	1.34(0.04,81.75)	1.34(0.05,80.23)	0.00(-0.09,0.03)
IM TE 200 mg/2wk		1.18(0.01,127.10)	1.18(0.01,115.70)	0.00(-0.09,0.12)
IM TE 250 mg/3 wk		0.83(0.01,129.40)	0.83(0.01,116.90)	0.00(-0.09,0.11)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.82(0.01,30.93)	0.82(0.01,27.50)	0.00(-0.02,0.12)
IM TE 250 mg/3 wk		0.63(0.02,15.34)	0.63(0.02,13.78)	0.00(-0.02,0.11)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	0.76(0.00,109.00)	0.76(0.01,101.30)	0.00(-0.12,0.11)

Prostate cancer, treatment duration 6 months or longer, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Gel 5 mg/d	Placebo	0.61(0.03,8.64)	0.61(0.03,7.65)	-0.01(-0.02,0.11)
Gel 1% 50 mg/d		0.63(0.07,4.07)	0.64(0.08,3.89)	-0.01(-0.02,0.05)
Gel 1% 100 mg/d		1.46(0.10,24.72)	1.45(0.10,17.93)	0.01(-0.02,0.26)
Oral TU 160 mg/d		0.17(0.00,1.97)	0.17(0.00,1.94)	-0.01(-0.03,0.02)
IM TU 1000 mg/12 wk		0.27(0.01,4.19)	0.28(0.01,3.97)	-0.01(-0.03,0.05)
IM TE 150 mg/2wk		0.41(0.05,2.85)	0.41(0.05,2.77)	-0.01(-0.02,0.03)
IM TE 200 mg/2wk		1.60(0.14,20.43)	1.58(0.14,15.66)	0.01(-0.02,0.24)
IM TE 250 mg/4wk		0.59(0.01,14.32)	0.60(0.01,11.82)	-0.01(-0.03,0.18)

Gel 1% 50 mg/d	Gel 5 mg/d	1.02(0.04,33.49)	1.02(0.04,32.09)	0.00(-0.12,0.05)
Gel 1% 100 mg/d		2.42(0.06,140.90)	2.36(0.07,114.10)	0.01(-0.10,0.26)
Oral TU 160 mg/d		0.27(0.00,13.67)	0.27(0.00,13.34)	-0.01(-0.12,0.03)
IM TU 1000 mg/12 wk		0.42(0.00,26.06)	0.43(0.01,24.75)	0.00(-0.12,0.06)
IM TE 150 mg/2wk		0.66(0.02,21.03)	0.66(0.02,20.38)	0.00(-0.12,0.04)
IM TE 200 mg/2wk		2.72(0.07,121.80)	2.64(0.07,101.90)	0.01(-0.10,0.24)
IM TE 250 mg/4wk		0.93(0.01,78.30)	0.94(0.01,66.83)	0.00(-0.11,0.18)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	2.36(0.10,71.99)	2.31(0.10,55.22)	0.01(-0.04,0.27)
Oral TU 160 mg/d		0.25(0.01,7.14)	0.26(0.01,6.97)	-0.01(-0.06,0.02)
IM TU 1000 mg/12 wk		0.42(0.01,13.09)	0.42(0.01,12.44)	-0.01(-0.06,0.06)
IM TE 150 mg/2wk		0.64(0.04,11.27)	0.65(0.04,10.94)	0.00(-0.06,0.04)
IM TE 200 mg/2wk		2.58(0.12,67.79)	2.53(0.12,54.73)	0.02(-0.04,0.24)
IM TE 250 mg/4wk		0.93(0.01,40.53)	0.93(0.01,33.69)	0.00(-0.05,0.18)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.11(0.00,4.64)	0.11(0.00,4.51)	-0.02(-0.28,0.02)
IM TU 1000 mg/12 wk		0.17(0.00,8.49)	0.18(0.00,8.04)	-0.02(-0.27,0.05)
IM TE 150 mg/2wk		0.27(0.01,7.46)	0.28(0.01,7.20)	-0.02(-0.27,0.03)
IM TE 200 mg/2wk		1.07(0.03,44.37)	1.07(0.03,36.46)	0.00(-0.25,0.23)
IM TE 250 mg/4wk		0.38(0.00,27.49)	0.39(0.00,23.11)	-0.01(-0.27,0.16)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.74(0.02,125.60)	1.73(0.02,120.10)	0.00(-0.03,0.07)
IM TE 150 mg/2wk		2.44(0.09,146.70)	2.43(0.09,142.50)	0.00(-0.03,0.05)
IM TE 200 mg/2wk		10.06(0.25,855.80)	9.66(0.26,694.90)	0.02(-0.02,0.25)
IM TE 250 mg/4wk		3.60(0.03,379.10)	3.55(0.03,320.80)	0.01(-0.03,0.19)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	1.51(0.05,86.89)	1.50(0.05,84.28)	0.00(-0.06,0.04)
IM TE 200 mg/2wk		6.21(0.15,510.50)	5.96(0.16,437.30)	0.02(-0.04,0.25)
IM TE 250 mg/4wk		2.16(0.02,282.30)	2.14(0.02,237.10)	0.00(-0.06,0.19)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	4.01(0.16,117.00)	3.88(0.17,94.62)	0.02(-0.03,0.25)
IM TE 250 mg/4wk		1.44(0.02,70.26)	1.43(0.02,57.58)	0.00(-0.04,0.18)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.35(0.00,21.02)	0.36(0.00,17.43)	-0.01(-0.24,0.16)

Serious adverse events, treatment duration 6 months or longer, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 4.8 mg/d	Placebo	0.29(0.01,7.30)	0.30(0.01,5.82)	-0.03(-0.05,0.20)
Gel 1% 50 mg/d		1.31(0.49,3.69)	1.29(0.51,3.35)	0.01(-0.02,0.09)
Gel 1% 100 mg/d		2.07(0.64,6.70)	1.98(0.65,5.46)	0.04(-0.02,0.18)
Gel 1.62% 40.5 mg/d		0.74(0.12,7.00)	0.75(0.13,5.82)	-0.01(-0.05,0.17)
Oral TU 160 mg/d		0.44(0.11,1.52)	0.45(0.12,1.49)	-0.02(-0.05,0.02)
IM TU 1000 mg/12 wk		0.39(0.10,1.37)	0.40(0.10,1.36)	-0.02(-0.05,0.01)
IM TE 250 mg/3 wk		0.42(0.02,8.65)	0.43(0.02,6.59)	-0.02(-0.05,0.23)
Gel 1% 50 mg/d	Patch 4.8 mg/d	4.48(0.16,127.10)	4.27(0.20,117.40)	0.04(-0.18,0.12)
Gel 1% 100 mg/d		7.11(0.23,206.90)	6.52(0.28,180.50)	0.06(-0.16,0.21)
Gel 1.62% 40.5 mg/d		2.74(0.06,118.10)	2.66(0.08,104.30)	0.02(-0.20,0.18)
Oral TU 160 mg/d		1.48(0.05,44.39)	1.47(0.07,42.99)	0.00(-0.22,0.05)
IM TU 1000 mg/12 wk		1.28(0.06,31.88)	1.28(0.07,31.17)	0.00(-0.21,0.04)
IM TE 250 mg/3 wk		1.48(0.26,6.80)	1.45(0.28,6.44)	0.00(-0.07,0.12)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.58(0.32,7.26)	1.53(0.34,6.04)	0.03(-0.07,0.17)
Gel 1.62% 40.5 mg/d		0.57(0.07,6.39)	0.58(0.07,5.35)	-0.02(-0.11,0.16)
Oral TU 160 mg/d		0.33(0.06,1.63)	0.35(0.07,1.59)	-0.03(-0.12,0.02)

IM TU 1000 mg/12 wk		0.29(0.05,1.43)	0.30(0.06,1.41)	-0.04(-0.12,0.01)
IM TE 250 mg/3 wk		0.32(0.01,7.49)	0.33(0.02,5.76)	-0.03(-0.12,0.21)
Gel 1.62% 40.5 mg/d	Gel 1% 100 mg/d	0.36(0.04,4.46)	0.38(0.05,3.85)	-0.05(-0.20,0.13)
Oral TU 160 mg/d		0.21(0.04,1.19)	0.23(0.04,1.18)	-0.06(-0.21,0.01)
IM TU 1000 mg/12 wk		0.19(0.03,1.04)	0.20(0.04,1.03)	-0.06(-0.21,0.00)
IM TE 250 mg/3 wk		0.20(0.01,5.17)	0.22(0.01,4.05)	-0.06(-0.20,0.18)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.58(0.04,5.55)	0.59(0.05,5.35)	-0.01(-0.18,0.04)
IM TU 1000 mg/12 wk		0.50(0.04,4.67)	0.51(0.05,4.54)	-0.01(-0.19,0.03)
IM TE 250 mg/3 wk		0.54(0.01,20.13)	0.55(0.02,15.36)	-0.01(-0.18,0.23)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.87(0.14,5.27)	0.87(0.15,5.13)	0.00(-0.05,0.03)
IM TE 250 mg/3 wk		1.00(0.04,23.45)	1.00(0.04,17.76)	0.00(-0.05,0.24)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	1.12(0.06,20.83)	1.12(0.06,16.04)	0.00(-0.03,0.24)

Withdrawals due to adverse events, treatment duration less than 6 months, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% Crl)	RR (95% Crl)	RD% (95% Crl)
Patch 5 mg/d	placebo	3.42(0.54,18.50)	3.10(0.55,11.46)	0.09(-0.02,0.38)
Gel 1% 50 mg/d		0.91(0.25,3.01)	0.92(0.26,2.81)	0.00(-0.04,0.07)
Gel 1% 75 mg/d		3.40(0.27,51.69)	3.08(0.27,18.15)	0.08(-0.03,0.63)
Gel 1% 100 mg/d		0.78(0.11,4.02)	0.79(0.11,3.61)	-0.01(-0.05,0.10)
Oral TU 120 mg/d		0.53(0.01,17.84)	0.55(0.01,10.94)	-0.02(-0.06,0.37)
Oral TU 160 mg/d		3.00(0.19,59.70)	2.77(0.20,19.66)	0.07(-0.04,0.66)
IM TU 1000 mg/12 wk		0.56(0.01,17.21)	0.57(0.01,10.67)	-0.02(-0.06,0.36)
IM TE 100 mg/wk		0.56(0.01,18.09)	0.57(0.01,11.06)	-0.02(-0.06,0.37)
IM TE 200 mg/2wk		2.23(0.15,27.83)	2.12(0.16,14.18)	0.05(-0.04,0.47)
Gel 1% 50 mg/d	Patch 5 mg/d	0.27(0.05,1.68)	0.30(0.07,1.63)	-0.09(-0.37,0.02)
Gel 1% 75 mg/d		1.00(0.05,26.46)	1.00(0.07,11.33)	0.00(-0.32,0.56)
Gel 1% 100 mg/d		0.23(0.03,1.71)	0.26(0.04,1.63)	-0.09(-0.36,0.03)
Oral TU 120 mg/d		0.15(0.00,8.66)	0.18(0.00,5.65)	-0.09(-0.39,0.30)
Oral TU 160 mg/d		0.89(0.04,29.95)	0.91(0.05,11.88)	-0.01(-0.33,0.59)
IM TU 1000 mg/12 wk		0.16(0.00,7.86)	0.19(0.00,5.37)	-0.09(-0.39,0.29)
IM TE 100 mg/wk		0.16(0.00,8.37)	0.19(0.00,5.62)	-0.09(-0.39,0.29)
IM TE 200 mg/2wk		0.66(0.05,8.46)	0.70(0.06,5.33)	-0.03(-0.29,0.34)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	3.76(0.23,79.09)	3.37(0.25,29.93)	0.09(-0.05,0.63)
Gel 1% 100 mg/d		0.85(0.11,5.57)	0.86(0.11,5.04)	0.00(-0.07,0.10)
Oral TU 120 mg/d		0.58(0.01,25.06)	0.60(0.01,15.19)	-0.01(-0.09,0.38)
Oral TU 160 mg/d		3.33(0.17,89.28)	3.02(0.19,31.43)	0.07(-0.06,0.66)
IM TU 1000 mg/12 wk		0.60(0.01,25.26)	0.61(0.01,15.72)	-0.01(-0.09,0.37)
IM TE 100 mg/wk		0.62(0.01,24.98)	0.63(0.01,15.59)	-0.01(-0.09,0.37)
IM TE 200 mg/2wk		2.43(0.15,37.00)	2.29(0.16,20.13)	0.05(-0.06,0.47)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	0.22(0.01,4.57)	0.25(0.02,4.26)	-0.09(-0.63,0.07)
Oral TU 120 mg/d		0.15(0.00,13.54)	0.18(0.00,9.14)	-0.08(-0.63,0.30)
Oral TU 160 mg/d		0.89(0.02,47.57)	0.91(0.04,20.95)	-0.01(-0.56,0.58)
IM TU 1000 mg/12 wk		0.15(0.00,12.34)	0.19(0.00,8.43)	-0.08(-0.63,0.29)
IM TE 100 mg/wk		0.16(0.00,12.51)	0.19(0.00,8.44)	-0.08(-0.63,0.29)
IM TE 200 mg/2wk		0.64(0.01,21.48)	0.69(0.03,13.84)	-0.03(-0.58,0.39)
Oral TU 120 mg/d	Gel 1% 100 mg/d	0.70(0.01,40.06)	0.71(0.01,25.14)	-0.01(-0.12,0.38)
Oral TU 160 mg/d		3.96(0.16,148.30)	3.53(0.18,57.23)	0.08(-0.08,0.66)
IM TU 1000 mg/12 wk		0.71(0.01,38.23)	0.72(0.01,24.56)	-0.01(-0.12,0.37)
IM TE 100 mg/wk		0.75(0.01,36.96)	0.75(0.01,23.88)	-0.01(-0.12,0.37)
IM TE 200 mg/2wk		2.93(0.15,58.47)	2.72(0.16,33.79)	0.05(-0.08,0.47)
Oral TU 160 mg/d	Oral TU 120 mg/d	5.89(0.07,791.50)	5.01(0.10,403.00)	0.07(-0.30,0.66)
IM TU 1000 mg/12 wk		0.99(0.00,212.40)	0.99(0.01,150.10)	0.00(-0.37,0.36)

IM TE 100 mg/wk		1.07(0.01,195.70)	1.06(0.01,142.30)	0.00(-0.37,0.37)
IM TE 200 mg/2wk		4.31(0.05,414.70)	3.87(0.07,289.70)	0.05(-0.33,0.48)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.18(0.00,13.64)	0.21(0.00,9.68)	-0.07(-0.66,0.29)
IM TE 100 mg/wk		0.18(0.00,15.17)	0.21(0.00,10.89)	-0.07(-0.65,0.29)
IM TE 200 mg/2wk		0.73(0.01,30.61)	0.77(0.03,19.20)	-0.02(-0.61,0.41)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.08(0.01,176.80)	1.07(0.01,129.60)	0.00(-0.37,0.36)
IM TE 200 mg/2wk		4.11(0.05,468.60)	3.68(0.07,313.30)	0.05(-0.32,0.48)
IM TE 200 mg/2wk	IM TE 100 mg/wk	4.03(0.05,414.60)	3.62(0.07,275.60)	0.05(-0.32,0.48)

Withdrawals due to adverse events, treatment duration 6 months or longer, continuity correction — Odds Ratios, Relative Risks and Risk Difference for All Treatment Comparisons (Random-Effects Model)

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD% (95% CrI)
Patch 5 mg/d	Placebo	0.25(0.01,3.68)	0.26(0.01,3.20)	-0.04(-0.07,0.12)
Gel 1% 5 mg/d		0.76(0.28,1.99)	0.77(0.30,1.89)	-0.01(-0.04,0.05)
Gel 1% 50 mg/d		0.89(0.41,1.90)	0.89(0.43,1.81)	-0.01(-0.04,0.05)
Gel 1% 100 mg/d		0.89(0.31,2.52)	0.89(0.32,2.32)	-0.01(-0.04,0.08)
Gel 1.62% 40.5 mg/d		8.59(1.29,134.20)	5.93(1.26,16.98)	0.29(0.02,0.83)
Gel 2% 60 mg/d		1.62(0.58,4.61)	1.57(0.59,3.81)	0.03(-0.02,0.16)
Oral TU 160 mg/d		0.84(0.29,2.35)	0.84(0.30,2.19)	-0.01(-0.04,0.07)
Oral TU 120-160 mg/d		0.53(0.01,12.28)	0.55(0.01,7.62)	-0.03(-0.07,0.36)
IM TU 1000 mg/12 wk		0.49(0.18,1.30)	0.51(0.19,1.28)	-0.03(-0.05,0.01)
IM TE 125 mg/wk		6.38(0.86,57.20)	4.83(0.87,14.34)	0.22(-0.01,0.72)
IM TE 150 mg/2 wk		0.79(0.04,10.60)	0.80(0.05,6.94)	-0.01(-0.06,0.32)
IM TE 200 mg/2wk		2.61(0.58,13.71)	2.39(0.60,8.15)	0.08(-0.02,0.39)
IM TE 250 mg/3wk		1.95(0.30,13.79)	1.84(0.31,8.15)	0.05(-0.04,0.39)
IM TE 250 mg/4 wk		1.50(0.17,17.85)	1.45(0.17,9.27)	0.03(-0.05,0.45)
IM TE 300 mg/3wk		0.66(0.11,3.75)	0.68(0.12,3.25)	-0.02(-0.06,0.13)
IM TE 50-400 mg/wk		0.57(0.01,15.72)	0.58(0.01,8.74)	-0.02(-0.07,0.42)
IM TC 200 mg/2 wk		4.60(0.63,41.23)	3.79(0.64,12.88)	0.16(-0.02,0.65)
Gel 1% 5 mg/d	Patch 5 mg/d	3.05(0.17,111.10)	2.95(0.20,104.40)	0.03(-0.13,0.10)
Gel 1% 50 mg/d		3.56(0.22,120.50)	3.42(0.26,113.20)	0.03(-0.13,0.09)
Gel 1% 100 mg/d		3.58(0.19,136.10)	3.43(0.22,124.90)	0.03(-0.13,0.12)
Gel 1.62% 40.5 mg/d		37.35(1.22,2493.00)	21.70(1.18,774.80)	0.32(0.02,0.86)
Gel 2% 60 mg/d		6.51(0.36,247.20)	5.94(0.40,216.40)	0.07(-0.09,0.21)
Oral TU 160 mg/d		3.34(0.18,118.60)	3.22(0.21,110.70)	0.03(-0.13,0.11)
Oral TU 120-160 mg/d		2.07(0.03,212.10)	2.01(0.03,151.50)	0.01(-0.14,0.40)
IM TU 1000 mg/12 wk		1.99(0.11,70.73)	1.96(0.13,68.00)	0.01(-0.15,0.06)
IM TE 125 mg/wk		25.95(0.86,1460.00)	17.20(0.88,647.50)	0.25(-0.01,0.75)
IM TE 150 mg/2 wk		3.12(0.06,245.60)	2.95(0.07,187.20)	0.02(-0.13,0.35)
IM TE 200 mg/2wk		10.54(0.45,457.30)	8.97(0.49,331.90)	0.11(-0.07,0.42)
IM TE 250 mg/3wk		7.94(0.30,377.00)	6.94(0.33,280.60)	0.08(-0.09,0.43)
IM TE 250 mg/4 wk		6.29(0.17,438.20)	5.66(0.20,276.10)	0.06(-0.11,0.49)
IM TE 300 mg/3wk		2.68(0.11,121.80)	2.60(0.13,110.40)	0.02(-0.14,0.16)
IM TE 50-400 mg/wk		2.38(0.02,250.90)	2.28(0.03,157.90)	0.01(-0.14,0.45)
IM TC 200 mg/2 wk		19.26(0.62,985.50)	13.97(0.66,499.60)	0.19(-0.04,0.69)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.18(0.34,4.06)	1.17(0.36,3.80)	0.01(-0.06,0.07)
Gel 1% 100 mg/d		1.17(0.28,4.94)	1.16(0.30,4.49)	0.01(-0.07,0.09)
Gel 1.62% 40.5 mg/d		11.49(1.33,200.30)	7.62(1.29,32.88)	0.30(0.02,0.84)
Gel 2% 60 mg/d		2.15(0.52,8.98)	2.04(0.55,7.51)	0.04(-0.04,0.18)
Oral TU 160 mg/d		1.10(0.26,4.53)	1.10(0.28,4.15)	0.00(-0.07,0.09)
Oral TU 120-160 mg/d		0.71(0.01,19.63)	0.72(0.02,12.03)	-0.01(-0.09,0.38)
IM TU 1000 mg/12 wk		0.65(0.16,2.60)	0.66(0.17,2.51)	-0.01(-0.08,0.03)
IM TE 125 mg/wk		8.48(0.89,93.51)	6.15(0.90,27.18)	0.23(-0.01,0.73)
IM TE 150 mg/2 wk		1.05(0.05,16.85)	1.05(0.05,10.93)	0.00(-0.08,0.34)

IM TE 200 mg/2wk		3.45(0.57,23.52)	3.09(0.60,14.57)	0.09(-0.03,0.40)
IM TE 250 mg/3wk		2.56(0.31,23.11)	2.38(0.33,13.96)	0.06(-0.05,0.41)
IM TE 250 mg/4 wk		1.97(0.18,28.25)	1.88(0.20,14.88)	0.04(-0.06,0.47)
IM TE 300 mg/3wk		0.87(0.12,6.50)	0.87(0.13,5.58)	-0.01(-0.08,0.14)
IM TE 50-400 mg/wk		0.76(0.02,24.24)	0.77(0.02,13.53)	-0.01(-0.09,0.43)
IM TC 200 mg/2 wk		6.06(0.65,66.60)	4.85(0.67,23.71)	0.17(-0.02,0.66)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.01(0.27,3.64)	1.01(0.28,3.33)	0.00(-0.06,0.09)
Gel 1.62% 40.5 mg/d		9.73(1.26,160.90)	6.56(1.24,24.49)	0.29(0.02,0.83)
Gel 2% 60 mg/d		1.84(0.51,6.67)	1.76(0.53,5.52)	0.04(-0.04,0.17)
Oral TU 160 mg/d		0.94(0.25,3.46)	0.94(0.27,3.18)	0.00(-0.07,0.08)
Oral TU 120-160 mg/d		0.60(0.01,16.04)	0.61(0.01,9.82)	-0.02(-0.09,0.37)
IM TU 1000 mg/12 wk		0.55(0.16,1.90)	0.57(0.17,1.85)	-0.02(-0.08,0.03)
IM TE 125 mg/wk		7.20(0.82,73.89)	5.35(0.83,20.08)	0.23(-0.01,0.72)
IM TE 150 mg/2 wk		0.89(0.05,13.11)	0.90(0.05,8.56)	0.00(-0.08,0.33)
IM TE 200 mg/2wk		2.94(0.53,18.41)	2.66(0.55,11.38)	0.08(-0.03,0.39)
IM TE 250 mg/3wk		2.20(0.30,17.34)	2.06(0.31,10.64)	0.05(-0.05,0.39)
IM TE 250 mg/4 wk		1.69(0.17,22.80)	1.62(0.18,12.13)	0.03(-0.06,0.46)
IM TE 300 mg/3wk		0.75(0.11,4.89)	0.76(0.12,4.22)	-0.01(-0.08,0.13)
IM TE 50-400 mg/wk		0.63(0.01,19.41)	0.64(0.02,10.80)	-0.02(-0.09,0.43)
IM TC 200 mg/2 wk		5.18(0.59,53.21)	4.20(0.61,18.00)	0.17(-0.03,0.66)
Gel 1.62% 40.5 mg/d	Gel 1% 100 mg/d	9.86(1.10,175.60)	6.55(1.09,30.02)	0.29(0.01,0.83)
Gel 2% 60 mg/d		1.84(0.42,8.24)	1.76(0.45,6.93)	0.04(-0.06,0.17)
Oral TU 160 mg/d		0.94(0.20,4.23)	0.95(0.22,3.89)	0.00(-0.09,0.08)
Oral TU 120-160 mg/d		0.61(0.01,16.76)	0.62(0.01,10.40)	-0.02(-0.11,0.37)
IM TU 1000 mg/12 wk		0.55(0.13,2.37)	0.57(0.15,2.30)	-0.02(-0.11,0.03)
IM TE 125 mg/wk		7.17(0.75,81.81)	5.28(0.77,24.80)	0.22(-0.02,0.72)
IM TE 150 mg/2 wk		0.91(0.04,14.61)	0.92(0.05,9.73)	0.00(-0.10,0.33)
IM TE 200 mg/2wk		2.96(0.46,21.06)	2.66(0.49,13.22)	0.08(-0.05,0.39)
IM TE 250 mg/3wk		2.23(0.25,20.18)	2.08(0.27,12.68)	0.05(-0.07,0.39)
IM TE 250 mg/4 wk		1.71(0.15,24.04)	1.65(0.16,13.23)	0.03(-0.08,0.45)
IM TE 300 mg/3wk		0.75(0.10,5.83)	0.76(0.10,5.07)	-0.01(-0.10,0.14)
IM TE 50-400 mg/wk		0.64(0.01,21.71)	0.65(0.02,12.20)	-0.02(-0.11,0.42)
IM TC 200 mg/2 wk		5.23(0.54,58.01)	4.20(0.57,21.54)	0.16(-0.04,0.66)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.19(0.01,1.65)	0.27(0.06,1.53)	-0.25(-0.79,0.05)
Oral TU 160 mg/d		0.10(0.01,0.83)	0.14(0.03,0.85)	-0.29(-0.84,-0.01)
Oral TU 120-160 mg/d		0.05(0.00,2.49)	0.09(0.00,1.96)	-0.28(-0.84,0.15)
IM TU 1000 mg/12 wk		0.06(0.00,0.47)	0.09(0.02,0.50)	-0.31(-0.86,-0.04)
IM TE 125 mg/wk		0.74(0.02,13.90)	0.82(0.11,5.40)	-0.06(-0.69,0.53)
IM TE 150 mg/2 wk		0.08(0.00,2.24)	0.14(0.01,1.86)	-0.28(-0.83,0.12)
IM TE 200 mg/2wk		0.30(0.01,3.85)	0.41(0.07,2.83)	-0.19(-0.78,0.22)
IM TE 250 mg/3wk		0.22(0.01,3.65)	0.32(0.04,2.63)	-0.22(-0.79,0.21)
IM TE 250 mg/4 wk		0.17(0.01,4.16)	0.25(0.02,2.78)	-0.24(-0.80,0.25)
IM TE 300 mg/3wk		0.07(0.00,1.03)	0.12(0.01,1.02)	-0.30(-0.84,0.00)
IM TE 50-400 mg/wk		0.06(0.00,3.14)	0.10(0.00,2.24)	-0.28(-0.84,0.20)
IM TC 200 mg/2 wk		0.51(0.02,10.62)	0.64(0.08,4.71)	-0.12(-0.72,0.47)
Oral TU 160 mg/d	Gel 2% 60 mg/d	0.51(0.11,2.24)	0.54(0.14,2.11)	-0.04(-0.18,0.05)
Oral TU 120-160 mg/d		0.32(0.01,9.15)	0.35(0.01,5.82)	-0.05(-0.19,0.33)
IM TU 1000 mg/12 wk		0.30(0.07,1.27)	0.32(0.08,1.25)	-0.06(-0.20,0.01)
IM TE 125 mg/wk		3.93(0.40,43.28)	3.03(0.45,13.42)	0.18(-0.08,0.68)
IM TE 150 mg/2 wk		0.49(0.02,7.70)	0.51(0.03,5.32)	-0.04(-0.19,0.29)
IM TE 200 mg/2wk		1.60(0.26,11.41)	1.51(0.29,7.41)	0.04(-0.12,0.36)
IM TE 250 mg/3wk		1.19(0.14,10.88)	1.17(0.16,6.81)	0.01(-0.15,0.36)
IM TE 250 mg/4 wk		0.93(0.08,13.60)	0.93(0.09,7.59)	-0.01(-0.16,0.42)
IM TE 300 mg/3wk		0.40(0.05,3.06)	0.43(0.06,2.71)	-0.05(-0.19,0.10)
IM TE 50-400 mg/wk		0.35(0.01,11.62)	0.37(0.01,6.72)	-0.05(-0.19,0.39)
IM TC 200 mg/2 wk		2.83(0.30,31.83)	2.38(0.34,11.80)	0.12(-0.10,0.62)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.64(0.01,18.46)	0.65(0.01,11.55)	-0.01(-0.10,0.37)

IM TU 1000 mg/12 wk		0.59(0.14,2.46)	0.60(0.15,2.37)	-0.02(-0.10,0.03)
IM TE 125 mg/wk		7.75(0.81,86.07)	5.66(0.83,25.80)	0.23(-0.01,0.72)
IM TE 150 mg/2 wk		0.95(0.04,15.09)	0.95(0.05,10.20)	0.00(-0.09,0.33)
IM TE 200 mg/2wk		3.15(0.50,21.53)	2.83(0.52,13.59)	0.09(-0.04,0.39)
IM TE 250 mg/3wk		2.34(0.26,22.45)	2.18(0.28,13.81)	0.06(-0.07,0.40)
IM TE 250 mg/4 wk		1.79(0.16,26.56)	1.72(0.17,14.50)	0.03(-0.08,0.46)
IM TE 300 mg/3wk		0.79(0.10,6.08)	0.80(0.11,5.27)	-0.01(-0.09,0.14)
IM TE 50-400 mg/wk		0.70(0.02,21.69)	0.71(0.02,12.15)	-0.01(-0.10,0.42)
IM TC 200 mg/2 wk		5.48(0.58,66.53)	4.40(0.60,23.90)	0.17(-0.03,0.66)
IM TU 1000 mg/12 wk	Oral TU 120-160 mg/d	0.92(0.03,42.33)	0.92(0.06,40.49)	0.00(-0.39,0.05)
IM TE 125 mg/wk		12.63(0.28,785.90)	8.45(0.38,363.60)	0.22(-0.19,0.73)
IM TE 150 mg/2 wk		1.45(0.02,132.60)	1.42(0.03,100.70)	0.01(-0.36,0.33)
IM TE 200 mg/2wk		4.91(0.15,293.90)	4.23(0.22,210.80)	0.09(-0.29,0.40)
IM TE 250 mg/3wk		3.62(0.09,282.60)	3.25(0.14,189.90)	0.06(-0.32,0.41)
IM TE 250 mg/4 wk		2.89(0.06,247.30)	2.66(0.09,167.00)	0.04(-0.32,0.46)
IM TE 300 mg/3wk		1.24(0.03,75.26)	1.23(0.05,67.73)	0.01(-0.38,0.15)
IM TE 50-400 mg/wk		1.10(0.01,170.80)	1.09(0.01,114.50)	0.00(-0.37,0.43)
IM TC 200 mg/2 wk		8.83(0.20,628.00)	6.53(0.28,327.70)	0.16(-0.23,0.66)
IM TE 125 mg/wk	IM TU 1000 mg/12 wk	13.21(1.35,148.00)	9.41(1.32,41.65)	0.25(0.01,0.75)
IM TE 150 mg/2 wk		1.62(0.08,25.01)	1.58(0.08,16.15)	0.02(-0.05,0.35)
IM TE 200 mg/2wk		5.36(0.87,35.65)	4.71(0.87,22.25)	0.11(-0.01,0.41)
IM TE 250 mg/3wk		3.97(0.54,31.48)	3.62(0.55,19.29)	0.08(-0.02,0.41)
IM TE 250 mg/4 wk		3.05(0.29,43.16)	2.87(0.30,23.14)	0.05(-0.03,0.48)
IM TE 300 mg/3wk		1.37(0.18,9.49)	1.36(0.18,8.03)	0.01(-0.04,0.16)
IM TE 50-400 mg/wk		1.16(0.03,36.05)	1.15(0.03,20.07)	0.00(-0.05,0.45)
IM TC 200 mg/2 wk		9.36(1.01,103.80)	7.35(1.01,35.85)	0.19(0.00,0.68)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.12(0.00,3.32)	0.17(0.01,2.62)	-0.21(-0.72,0.16)
IM TE 200 mg/2wk		0.41(0.03,5.66)	0.51(0.08,4.04)	-0.13(-0.65,0.26)
IM TE 250 mg/3wk		0.30(0.02,5.30)	0.39(0.05,3.85)	-0.16(-0.67,0.25)
IM TE 250 mg/4 wk		0.23(0.01,5.19)	0.32(0.03,3.49)	-0.17(-0.69,0.27)
IM TE 300 mg/3wk		0.10(0.01,1.51)	0.15(0.02,1.44)	-0.23(-0.73,0.03)
IM TE 50-400 mg/wk		0.09(0.00,4.41)	0.13(0.00,2.96)	-0.21(-0.73,0.24)
IM TC 200 mg/2 wk		0.70(0.04,13.20)	0.78(0.10,6.29)	-0.06(-0.60,0.49)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.29(0.17,89.26)	2.91(0.24,63.45)	0.08(-0.25,0.39)
IM TE 250 mg/3wk		2.48(0.10,79.48)	2.27(0.14,54.34)	0.05(-0.28,0.40)
IM TE 250 mg/4 wk		1.98(0.07,76.59)	1.87(0.09,49.61)	0.03(-0.29,0.45)
IM TE 300 mg/3wk		0.84(0.04,25.16)	0.84(0.06,22.35)	-0.01(-0.33,0.15)
IM TE 50-400 mg/wk		0.72(0.01,59.92)	0.74(0.01,39.40)	-0.01(-0.32,0.41)
IM TC 200 mg/2 wk		5.90(0.23,192.50)	4.53(0.29,95.17)	0.15(-0.20,0.65)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	0.75(0.06,8.84)	0.78(0.09,5.82)	-0.03(-0.35,0.32)
IM TE 250 mg/4 wk		0.57(0.04,10.68)	0.62(0.05,6.09)	-0.05(-0.36,0.38)
IM TE 300 mg/3wk		0.25(0.02,2.50)	0.29(0.03,2.29)	-0.09(-0.40,0.07)
IM TE 50-400 mg/wk		0.22(0.00,8.65)	0.25(0.00,5.37)	-0.09(-0.40,0.35)
IM TC 200 mg/2 wk		1.77(0.13,27.17)	1.57(0.18,10.60)	0.07(-0.28,0.59)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.77(0.04,17.35)	0.80(0.06,10.37)	-0.02(-0.37,0.41)
IM TE 300 mg/3wk		0.34(0.02,4.14)	0.37(0.04,3.72)	-0.06(-0.40,0.10)
IM TE 50-400 mg/wk		0.28(0.00,13.36)	0.32(0.01,8.47)	-0.06(-0.40,0.37)
IM TC 200 mg/2 wk		2.35(0.14,44.09)	1.99(0.20,19.02)	0.10(-0.28,0.61)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.44(0.02,6.88)	0.47(0.04,6.11)	-0.04(-0.47,0.12)
IM TE 50-400 mg/wk		0.37(0.00,22.03)	0.40(0.01,14.05)	-0.04(-0.47,0.38)
IM TC 200 mg/2 wk		3.16(0.12,63.54)	2.57(0.18,29.44)	0.12(-0.33,0.62)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.84(0.01,35.23)	0.84(0.02,21.72)	0.00(-0.15,0.43)
IM TC 200 mg/2 wk		7.05(0.48,111.90)	5.45(0.52,47.56)	0.17(-0.06,0.66)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	8.04(0.16,617.30)	5.99(0.25,332.80)	0.16(-0.29,0.66)

APPENDIX 9: COMPARISON OF ODDS RATIOS FOR HARMS OUTCOMES UNDER THE RANDOM- AND FIXED-EFFECTS MODELS

Cardiovascular death, base case (no continuity correction): Odds ratio (95% CrI) — random-effects and fixed effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Gel 1% 50 mg/d	Placebo	3.54 (0.67, 23.88)	3.41 (0.69, 21.34)
1% gel, 100 mg/d		1.66 (0.05, 46.10)	1.61 (0.07, 40.47)
1.62% gel, 40.5 mg/d		0.09 (0.00, 6.18)	0.09 (0.00, 5.33)
2% gel, 60 mg/d		0.10 (0.00, 3.45)	0.09 (0.00, 2.72)
Oral TU 120 mg/d		0.24 (0.00, 18.95)	0.22 (0.00, 15.81)
Oral TU 120 or 160 mg/d		0.22 (0.00, 13.93)	0.19 (0.00, 11.94)
IM TU 1000 mg/12 wk		0.53 (0.08, 2.74)	0.53 (0.09, 2.60)
IM TE 200 mg/2wk		0.15 (0.00, 5.82)	0.13 (0.00, 5.46)
IM TE 250 mg/3 wk		0.15 (0.00, 13.07)	0.16 (0.00, 12.73)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.48 (0.01, 18.20)	0.47 (0.01, 16.89)
1.62% gel, 40.5 mg/d		0.02 (0.00, 2.11)	0.02 (0.00, 2.05)
2% gel, 60 mg/d		0.03 (0.00, 1.57)	0.03 (0.00, 1.20)
Oral TU 120 mg/d		0.06 (0.00, 6.72)	0.06 (0.00, 6.26)
Oral TU 120 or 160 mg/d		0.06 (0.00, 5.48)	0.05 (0.00, 4.72)
IM TU 1000 mg/12 wk		0.14 (0.01, 1.67)	0.15 (0.01, 1.48)
IM TE 200 mg/2wk		0.04 (0.00, 2.30)	0.04 (0.00, 2.17)
IM TE 250 mg/3 wk		0.04 (0.00, 4.60)	0.04 (0.00, 4.92)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.05 (0.00, 12.34)	0.05 (0.00, 9.55)
2% gel, 60 mg/d		0.06 (0.00, 10.53)	0.05 (0.00, 5.97)
Oral TU 120 mg/d		0.14 (0.00, 43.77)	0.13 (0.00, 26.82)
Oral TU 120 or 160 mg/d		0.13 (0.00, 27.64)	0.11 (0.00, 21.30)
IM TU 1000 mg/12 wk		0.32 (0.01, 13.40)	0.32 (0.01, 11.07)
IM TE 200 mg/2wk		0.08 (0.00, 13.95)	0.08 (0.00, 11.11)
IM TE 250 mg/3 wk		0.09 (0.00, 24.03)	0.09 (0.00, 21.40)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	1.12 (0.00, 401.30)	1.01 (0.00, 393.30)
Oral TU 120 mg/d		2.61 (0.00, 1684.00)	2.47 (0.00, 1573.00)
Oral TU 120 or 160 mg/d		2.56 (0.00, 1471.00)	2.17 (0.00, 1303.00)
IM TU 1000 mg/12 wk		6.03 (0.06, 985.20)	6.12 (0.07, 1004.00)
IM TE 200 mg/2wk		1.65 (0.00, 760.10)	1.47 (0.00, 721.40)
IM TE 250 mg/3 wk		1.91 (0.00, 1186.00)	1.85 (0.00, 1254.00)
Oral TU 120 mg/d	2% gel, 60 mg/d	2.47 (0.00, 1683.00)	2.46 (0.00, 1586.00)
Oral TU 120 or 160 mg/d		2.43 (0.01, 1283.00)	2.12 (0.00, 1243.00)
IM TU 1000 mg/12 wk		5.33 (0.11, 979.60)	5.67 (0.12, 970.60)
IM TE 200 mg/2wk		1.49 (0.00, 781.70)	1.44 (0.00, 615.10)
IM TE 250 mg/3 wk		1.76 (0.00, 999.40)	1.82 (0.00, 1141.00)

Oral TU 120 or 160 mg/d	Oral TU 120 mg/d	0.93 (0.00, 663.40)	0.87 (0.00, 743.00)
IM TU 1000 mg/12 wk		2.25 (0.02, 784.60)	2.43 (0.02, 615.10)
IM TE 200 mg/2wk		0.58 (0.00, 673.10)	0.59 (0.00, 392.10)
IM TE 250 mg/3 wk		0.72 (0.00, 718.60)	0.76 (0.00, 680.40)
IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	2.37 (0.03, 489.20)	2.76 (0.03, 658.40)
IM TE 200 mg/2wk		0.74 (0.00, 278.60)	0.67 (0.00, 419.80)
IM TE 250 mg/3 wk		0.77 (0.00, 596.10)	0.87 (0.00, 719.00)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.30 (0.00, 18.63)	0.25 (0.00, 15.40)
IM TE 250 mg/3 wk		0.30 (0.00, 23.49)	0.32 (0.00, 24.21)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	1.26 (0.00, 647.50)	1.29 (0.00, 921.50)
Residual Deviance		22.7 (30 points)	22.92 (30 points)
DIC		57.24	57.15

Cardiovascular death, continuity correction: Odds ratio (95% CrI) — random-effects and fixed effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Gel 1% 50 mg/d	Placebo	2.42 (0.63, 11.80)	2.45 (0.64, 10.71)
1% gel, 100 mg/d		1.52 (0.11, 22.14)	1.48 (0.11, 21.51)
1.62% gel, 40.5 mg/d		0.36 (0.01, 9.95)	0.34 (0.01, 9.95)
2% gel, 60 mg/d		0.24 (0.01, 3.53)	0.26 (0.01, 3.41)
Oral TU 120 mg/d		0.50 (0.01, 11.87)	0.56 (0.01, 13.13)
Oral TU 120 or 160 mg/d		0.49 (0.01, 13.46)	0.52 (0.01, 11.20)
IM TU 1000 mg/12 wk		0.66 (0.15, 2.59)	0.66 (0.16, 2.51)
IM TE 200 mg/2wk		0.53 (0.04, 6.33)	0.58 (0.03, 6.45)
IM TE 250 mg/3 wk		0.41 (0.01, 13.71)	0.41 (0.01, 11.93)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.61 (0.03, 13.11)	0.60 (0.03, 12.23)
1.62% gel, 40.5 mg/d		0.14 (0.00, 5.29)	0.14 (0.00, 5.23)
2% gel, 60 mg/d		0.09 (0.00, 2.04)	0.10 (0.00, 1.99)
Oral TU 120 mg/d		0.20 (0.00, 5.83)	0.22 (0.00, 7.29)
Oral TU 120 or 160 mg/d		0.19 (0.00, 7.52)	0.20 (0.00, 5.99)
IM TU 1000 mg/12 wk		0.26 (0.03, 1.88)	0.27 (0.04, 1.82)
IM TE 200 mg/2wk		0.21 (0.01, 3.85)	0.23 (0.01, 3.73)
IM TE 250 mg/3 wk		0.16 (0.00, 7.15)	0.16 (0.00, 6.28)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.23 (0.00, 14.45)	0.23 (0.00, 15.28)
2% gel, 60 mg/d		0.14 (0.00, 6.92)	0.16 (0.00, 6.80)
Oral TU 120 mg/d		0.32 (0.00, 18.43)	0.36 (0.00, 22.07)
Oral TU 120 or 160 mg/d		0.30 (0.00, 24.13)	0.34 (0.00, 18.90)
IM TU 1000 mg/12 wk		0.43 (0.02, 8.29)	0.44 (0.02, 7.89)
IM TE 200 mg/2wk		0.34 (0.01, 13.52)	0.38 (0.01, 13.13)
IM TE 250 mg/3 wk		0.27 (0.00, 18.98)	0.27 (0.00, 18.89)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	0.60 (0.01, 44.76)	0.70 (0.01, 45.37)
Oral TU 120 mg/d		1.36 (0.01, 136.10)	1.53 (0.01, 142.30)
Oral TU 120 or 160 mg/d		1.32 (0.01, 140.70)	1.43 (0.01, 120.70)

IM TU 1000 mg/12 wk		1.86 (0.04, 52.83)	1.92 (0.05, 59.35)
IM TE 200 mg/2wk		1.43 (0.02, 74.77)	1.60 (0.02, 91.26)
IM TE 250 mg/3 wk		1.09 (0.01, 115.70)	1.15 (0.01, 124.60)
Oral TU 120 mg/d	2% gel, 60 mg/d	2.10 (0.02, 267.90)	2.22 (0.02, 233.50)
Oral TU 120 or 160 mg/d		2.16 (0.02, 214.70)	2.04 (0.02, 204.70)
IM TU 1000 mg/12 wk		2.82 (0.12, 115.90)	2.55 (0.13, 111.70)
IM TE 200 mg/2wk		2.29 (0.05, 149.80)	2.28 (0.05, 152.30)
IM TE 250 mg/3 wk		1.86 (0.01, 195.60)	1.65 (0.02, 199.40)
Oral TU 120 or 160 mg/d	Oral TU 120 mg/d	0.97 (0.01, 170.70)	0.91 (0.01, 120.10)
IM TU 1000 mg/12 wk		1.29 (0.04, 85.74)	1.19 (0.04, 61.81)
IM TE 200 mg/2wk		1.06 (0.02, 117.80)	1.04 (0.02, 89.02)
IM TE 250 mg/3 wk		0.85 (0.00, 157.40)	0.76 (0.01, 110.00)
IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	1.41 (0.03, 88.29)	1.29 (0.04, 67.74)
IM TE 200 mg/2wk		1.12 (0.01, 109.30)	1.13 (0.02, 92.41)
IM TE 250 mg/3 wk		0.86 (0.01, 143.80)	0.81 (0.01, 120.00)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.82 (0.04, 14.18)	0.87 (0.04, 14.09)
IM TE 250 mg/3 wk		0.64 (0.01, 18.85)	0.64 (0.01, 16.31)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	0.79 (0.01, 61.29)	0.71 (0.01, 56.02)
Residual Deviance		21.37(30 points)	21.32 (30 points)
DIC		92.19	91.811

Cardiovascular death, continuity correction, treatments with zero arms dropped: Odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Gel 1% 50 mg/d	Placebo	2.43 (0.59, 11.54)	2.45 (0.65, 10.55)
1% gel, 100 mg/d		1.49 (0.10, 21.29)	1.48 (0.11, 20.78)
IM TU 1000 mg/12 wk		0.62 (0.09, 3.42)	0.60 (0.11, 2.96)
1% gel, 100 mg/d	Gel 1% 50 mg/d	0.60 (0.03, 12.84)	0.60 (0.03, 11.65)
IM TU 1000 mg/12 wk		0.25 (0.02, 2.31)	0.24 (0.03, 1.93)
IM TU 1000 mg/12 wk	1% gel, 100 mg/d	0.42 (0.02, 10.50)	0.40 (0.02, 8.19)
Residual Deviance		11.14 (14 points)	11.15 (14 points)
DIC		46.42	46.07

Myocardial infarction, base case (no continuity correction): Odds ratio (95% CrI) — random-effects and fixed effects models

Treatment	Reference	Random-effects	Fixed-effects
Gel 1%, 5 mg/d	Placebo	0.08 (0.00, 3.23)	0.09 (0.00, 2.61)
Gel 1%, 50 mg/d		0.08 (0.00, 2.96)	0.09 (0.00, 2.62)
Gel 1%, 100 mg/d		3.25 (0.20, 73.74)	3.43 (0.28, 68.78)
Gel 1.62%, 40.5 mg/d		0.56 (0.02, 18.65)	0.49 (0.02, 15.85)
Gel 2%, 60 mg/d		0.10 (0.00, 3.38)	0.09 (0.00, 2.85)
Oral TU 160 mg/d		0.11 (0.00, 5.49)	0.13 (0.00, 5.31)
IM TU, 1000 mg/12 wk		0.18 (0.02, 1.00)	0.21 (0.03, 0.97)

IM TE, 200 mg/2wk		0.22 (0.00, 15.78)	0.22 (0.00, 15.25)
Gel 1%, 50 mg/d	Gel 1%, 5 mg/d	1.01 (0.00, 408.50)	1.00 (0.00, 364.50)
Gel 1%, 100 mg/d		43.78 (0.39, 13850.00)	43.68 (0.54, 10600.00)
Gel 1.62%, 40.5 mg/d		7.46 (0.05, 2541.00)	6.23 (0.06, 2078.00)
Gel 2%, 60 mg/d		1.12 (0.00, 376.00)	1.08 (0.00, 378.80)
Oral TU 160 mg/d		1.38 (0.00, 498.00)	1.54 (0.00, 647.20)
IM TU, 1000 mg/12 wk		2.18 (0.03, 380.00)	2.35 (0.05, 345.10)
IM TE, 200 mg/2wk		2.82 (0.01, 1437.00)	2.55 (0.00, 1436.00)
Gel 1%, 100 mg/d	Gel 1%, 50 mg/d	41.26 (0.39, 12040.00)	43.63 (0.54, 10800.00)
Gel 1.62%, 40.5 mg/d		6.95 (0.05, 2349.00)	6.20 (0.05, 2065.00)
Gel 2%, 60 mg/d		1.15 (0.00, 380.90)	1.08 (0.00, 391.30)
Oral TU 160 mg/d		1.40 (0.00, 540.70)	1.56 (0.00, 667.80)
IM TU, 1000 mg/12 wk		2.15 (0.03, 348.20)	2.34 (0.05, 374.90)
IM TE, 200 mg/2wk		2.68 (0.00, 1694.00)	2.54 (0.00, 1496.00)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.16 (0.00, 14.67)	0.14 (0.00, 9.89)
Gel 2%, 60 mg/d		0.03 (0.00, 2.80)	0.02 (0.00, 2.03)
Oral TU 160 mg/d		0.03 (0.00, 4.73)	0.03 (0.00, 3.71)
IM TU, 1000 mg/12 wk		0.05 (0.00, 1.43)	0.06 (0.00, 1.16)
IM TE, 200 mg/2wk		0.06 (0.00, 12.33)	0.06 (0.00, 9.11)
Gel 2%, 60 mg/d	Gel 1.62%, 40.5 mg/d	0.17 (0.00, 21.67)	0.17 (0.00, 19.95)
Oral TU 160 mg/d		0.19 (0.00, 33.68)	0.24 (0.00, 36.07)
IM TU, 1000 mg/12 wk		0.31 (0.01, 12.85)	0.40 (0.01, 13.38)
IM TE, 200 mg/2wk		0.38 (0.00, 81.30)	0.40 (0.00, 90.47)
Oral TU 160 mg/d	Gel 2%, 60 mg/d	1.18 (0.00, 701.70)	1.44 (0.00, 664.30)
IM TU, 1000 mg/12 wk		1.88 (0.03, 494.50)	2.17 (0.04, 357.40)
IM TE, 200 mg/2wk		2.34 (0.00, 1989.00)	2.36 (0.00, 1459.00)
IM TU, 1000 mg/12 wk	Oral TU 160 mg/d	1.52 (0.02, 289.00)	1.49 (0.03, 284.30)
IM TE, 200 mg/2wk		2.11 (0.00, 1422.00)	1.63 (0.00, 1183.00)
IM TE, 200 mg/2wk	IM TU, 1000 mg/12 wk	1.26 (0.00, 150.60)	1.05 (0.00, 108.60)
Residual Deviance		18.58	19.72
DIC		52.23	53.12

Myocardial infarction, continuity correction: Odds ratio (95% CrI) — random-effects and fixed effects models

Treatment	Reference	Random-effects	Fixed-effects
Gel 1%, 5 mg/d	Placebo	0.26 (0.01, 4.18)	0.26 (0.01, 3.45)
Gel 1%, 50 mg/d		0.25 (0.01, 4.13)	0.26 (0.01, 3.24)
Gel 1%, 100 mg/d		2.45 (0.23, 38.53)	2.55 (0.30, 31.68)
Gel 1.62%, 40.5 mg/d		0.73 (0.05, 15.62)	0.69 (0.05, 15.40)
Gel 2%, 60 mg/d		0.26 (0.01, 3.72)	0.27 (0.01, 3.46)
Oral TU 160 mg/d		0.50 (0.01, 8.96)	0.47 (0.01, 7.60)
IM TU, 1000 mg/12 wk		0.27 (0.05, 1.03)	0.27 (0.06, 1.00)
IM TE, 200 mg/2wk		0.54 (0.01, 14.15)	0.56 (0.01, 13.03)
Gel 1%, 50 mg/d	Gel 1%, 5 mg/d	0.98 (0.01, 68.23)	0.97 (0.01, 74.77)
Gel 1%, 100 mg/d		10.11 (0.24, 785.80)	10.37 (0.33, 669.50)
Gel 1.62%, 40.5 mg/d		3.04 (0.06, 239.00)	2.92 (0.07, 268.00)
Gel 2%, 60 mg/d		1.01 (0.01, 74.16)	0.99 (0.01, 76.69)
Oral TU 160 mg/d		1.86 (0.02, 175.70)	1.80 (0.02, 156.20)

IM TU, 1000 mg/12 wk		1.01 (0.04, 44.17)	1.01 (0.05, 42.73)
IM TE, 200 mg/2wk		2.10 (0.02, 257.40)	2.13 (0.02, 222.10)
Gel 1%, 100 mg/d	Gel 1%, 50 mg/d	10.90 (0.25, 1078.00)	10.81 (0.35, 708.90)
Gel 1.62%, 40.5 mg/d		3.24 (0.05, 327.40)	2.98 (0.07, 277.40)
Gel 2%, 60 mg/d		1.07 (0.01, 99.67)	1.03 (0.01, 77.91)
Oral TU 160 mg/d		2.07 (0.02, 205.90)	1.86 (0.02, 151.20)
IM TU, 1000 mg/12 wk		1.06 (0.04, 56.73)	1.05 (0.05, 42.44)
IM TE, 200 mg/2wk		2.17 (0.02, 286.80)	2.25 (0.02, 228.00)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.29 (0.01, 14.45)	0.27 (0.01, 11.92)
Gel 2%, 60 mg/d		0.10 (0.00, 3.75)	0.10 (0.00, 3.05)
Oral TU 160 mg/d		0.19 (0.00, 8.32)	0.17 (0.00, 6.27)
IM TU, 1000 mg/12 wk		0.10 (0.00, 1.74)	0.10 (0.01, 1.25)
IM TE, 200 mg/2wk		0.20 (0.00, 11.82)	0.20 (0.00, 9.48)
Gel 2%, 60 mg/d	Gel 1.62%, 40.5 mg/d	0.33 (0.00, 17.20)	0.35 (0.00, 14.41)
Oral TU 160 mg/d		0.66 (0.01, 34.63)	0.62 (0.01, 29.96)
IM TU, 1000 mg/12 wk		0.35 (0.01, 7.30)	0.37 (0.01, 6.89)
IM TE, 200 mg/2wk		0.70 (0.00, 48.97)	0.74 (0.01, 46.63)
Oral TU 160 mg/d	Gel 2%, 60 mg/d	1.98 (0.02, 205.10)	1.79 (0.02, 157.90)
IM TU, 1000 mg/12 wk		1.04 (0.04, 51.62)	1.02 (0.05, 43.68)
IM TE, 200 mg/2wk		2.14 (0.02, 260.50)	2.19 (0.02, 226.90)
IM TU, 1000 mg/12 wk	Oral TU 160 mg/d	0.52 (0.03, 20.35)	0.56 (0.03, 25.57)
IM TE, 200 mg/2wk		1.07 (0.01, 114.80)	1.23 (0.01, 148.10)
IM TE, 200 mg/2wk	IM TU, 1000 mg/12 wk	2.01 (0.03, 73.92)	2.10 (0.04, 67.14)
Residual Deviance		18.72 (21 points)	19.29 (21 points)
DIC		71.65	71.82

Myocardial infarction, continuity correction, treatments with zero arms dropped: Odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Gel 1%, 100 mg/d	Placebo	2.56 (0.25, 35.03)	2.48 (0.29, 29.64)
Gel 1.62%, 40.5 mg/d		0.72 (0.05, 16.19)	0.70 (0.05, 17.30)
IM TU, 1000 mg/12 wk		0.43 (0.08, 2.08)	0.42 (0.09, 1.77)
Gel 1.62%, 40.5 mg/d	Gel 1%, 100 mg/d	0.28 (0.01, 13.92)	0.28 (0.01, 13.13)
IM TU, 1000 mg/12 wk		0.17 (0.01, 2.72)	0.17 (0.01, 2.22)
IM TU, 1000 mg/12 wk	Gel 1.62%, 40.5 mg/d	0.58 (0.02, 13.51)	0.58 (0.02, 11.50)
Residual Deviance		9.12 (10 points)	9.45 (10 points)
DIC		35.83	35.96

Prostate cancer, base case (no continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	7.36 (0.66, 129.00)	3.18 (0.43, 25.40)
Gel 5 mg/d		0.96 (0.04, 22.24)	0.63 (0.04, 7.82)
Gel 1% 50 mg/d		0.66 (0.04, 8.90)	0.34 (0.02, 2.42)

Gel 1% 100 mg/d		1.41 (0.06, 32.28)	0.63 (0.04, 5.87)
Oral TU 160 mg/d		0.08 (0.00, 2.11)	0.06 (0.00, 1.28)
IM TU 1000 mg/12 wk		0.14 (0.00, 6.83)	0.10 (0.00, 2.83)
IM TE 150 mg/2wk		0.45 (0.05, 3.76)	0.42 (0.06, 2.33)
IM TE 200 mg/2wk		5.99 (0.65, 91.39)	2.72 (0.42, 21.09)
IM TE 250 mg/4wk		0.99 (0.00, 438.50)	0.21 (0.00, 15.25)
Gel 5 mg/d	Patch 5 mg/d	0.12 (0.00, 6.93)	0.19 (0.01, 4.88)
Gel 1% 50 mg/d		0.09 (0.00, 2.21)	0.10 (0.00, 1.42)
Gel 1% 100 mg/d		0.20 (0.00, 4.60)	0.20 (0.01, 2.71)
Oral TU 160 mg/d		0.01 (0.00, 0.67)	0.02 (0.00, 0.78)
IM TU 1000 mg/12 wk		0.02 (0.00, 1.93)	0.03 (0.00, 1.60)
IM TE 150 mg/2wk		0.06 (0.00, 1.53)	0.13 (0.01, 1.93)
IM TE 200 mg/2wk		0.84 (0.07, 9.18)	0.87 (0.12, 6.27)
IM TE 250 mg/4wk		0.12 (0.00, 94.67)	0.06 (0.00, 7.72)
Gel 1% 50 mg/d	Gel 5 mg/d	0.70 (0.01, 37.31)	0.53 (0.01, 17.34)
Gel 1% 100 mg/d		1.54 (0.02, 119.30)	0.99 (0.02, 35.28)
Oral TU 160 mg/d		0.07 (0.00, 7.20)	0.09 (0.00, 6.57)
IM TU 1000 mg/12 wk		0.14 (0.00, 21.32)	0.15 (0.00, 13.60)
IM TE 150 mg/2wk		0.46 (0.01, 22.35)	0.67 (0.03, 18.07)
IM TE 200 mg/2wk		6.74 (0.12, 347.60)	4.43 (0.19, 140.70)
IM TE 250 mg/4wk		0.98 (0.00, 1017.00)	0.33 (0.00, 55.49)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	2.17 (0.05, 110.80)	1.87 (0.06, 53.81)
Oral TU 160 mg/d		0.11 (0.00, 9.33)	0.18 (0.00, 10.72)
IM TU 1000 mg/12 wk		0.21 (0.00, 25.28)	0.29 (0.00, 20.96)
IM TE 150 mg/2wk		0.67 (0.02, 22.70)	1.27 (0.08, 29.88)
IM TE 200 mg/2wk		9.28 (0.35, 414.10)	8.32 (0.57, 210.40)
IM TE 250 mg/4wk		1.51 (0.00, 1268.00)	0.65 (0.00, 93.20)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.05 (0.00, 5.41)	0.09 (0.00, 6.27)
IM TU 1000 mg/12 wk		0.09 (0.00, 15.41)	0.15 (0.00, 12.40)
IM TE 150 mg/2wk		0.31 (0.01, 13.41)	0.67 (0.03, 17.95)
IM TE 200 mg/2wk		4.29 (0.14, 198.70)	4.39 (0.28, 119.00)
IM TE 250 mg/4wk		0.67 (0.00, 623.00)	0.34 (0.00, 55.23)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.96 (0.00, 726.20)	1.62 (0.00, 493.10)
IM TE 150 mg/2wk		6.03 (0.11, 971.10)	7.08 (0.18, 943.80)
IM TE 200 mg/2wk		89.45 (1.36, 19420.00)	48.00 (1.18, 6, 842.00)
IM TE 250 mg/4wk		12.97 (0.01, 32540.00)	3.71 (0.01, 1, 819.00)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	3.33 (0.04, 741.00)	4.45 (0.08, 768.40)
IM TE 200 mg/2wk		47.38 (0.46, 11490.00)	29.77 (0.57, 5, 463.00)
IM TE 250 mg/4wk		7.98 (0.00, 13500.00)	2.35 (0.00, 1, 338.00)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	13.84 (0.59, 429.50)	6.59 (0.50, 110.50)
IM TE 250 mg/4wk		2.20 (0.00, 1325.00)	0.50 (0.00, 54.57)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.15 (0.00, 105.70)	0.07 (0.00, 8.36)
Residual deviance			
DIC			

Prostate cancer, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	2.63 (0.38, 20.55)	2.75 (0.44, 18.28)
Gel 5 mg/d		0.61 (0.03, 9.09)	0.64 (0.04, 7.95)
Gel 1% 50 mg/d		0.56 (0.09, 2.87)	0.57 (0.09, 2.59)
Gel 1% 100 mg/d		0.81 (0.09, 6.07)	0.80 (0.09, 5.12)
Oral TU 160 mg/d		0.17 (0.01, 2.18)	0.17 (0.01, 1.74)
IM TU 1000 mg/12 wk		0.27 (0.01, 4.12)	0.26 (0.01, 3.42)
IM TE 150 mg/2wk		0.44 (0.05, 3.15)	0.43 (0.06, 2.37)
IM TE 200 mg/2wk		2.54 (0.37, 18.99)	2.52 (0.41, 18.63)
IM TE 250 mg/4wk		0.53 (0.01, 13.77)	0.55 (0.01, 13.08)
Gel 5 mg/d	Patch 5 mg/d	0.23 (0.01, 6.19)	0.23 (0.01, 5.15)
Gel 1% 50 mg/d		0.21 (0.02, 2.14)	0.20 (0.02, 1.84)
Gel 1% 100 mg/d		0.31 (0.02, 3.21)	0.29 (0.02, 2.73)
Oral TU 160 mg/d		0.06 (0.00, 1.74)	0.06 (0.00, 1.23)
IM TU 1000 mg/12 wk		0.10 (0.00, 2.94)	0.09 (0.00, 2.28)
IM TE 150 mg/2wk		0.16 (0.01, 2.66)	0.15 (0.01, 1.88)
IM TE 200 mg/2wk		0.96 (0.13, 7.14)	0.94 (0.13, 6.30)
IM TE 250 mg/4wk		0.19 (0.00, 7.63)	0.19 (0.00, 7.90)
Gel 1% 50 mg/d	Gel 5 mg/d	0.93 (0.04, 23.22)	0.88 (0.04, 22.46)
Gel 1% 100 mg/d		1.35 (0.04, 49.21)	1.26 (0.05, 37.45)
Oral TU 160 mg/d		0.28 (0.00, 12.88)	0.26 (0.00, 10.90)
IM TU 1000 mg/12 wk		0.43 (0.00, 21.55)	0.40 (0.01, 18.81)
IM TE 150 mg/2wk		0.72 (0.03, 26.81)	0.66 (0.03, 18.72)
IM TE 200 mg/2wk		4.27 (0.15, 144.50)	4.12 (0.18, 121.30)
IM TE 250 mg/4wk		0.83 (0.01, 61.46)	0.85 (0.01, 60.15)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.45 (0.10, 20.24)	1.41 (0.11, 17.38)
Oral TU 160 mg/d		0.31 (0.01, 6.23)	0.30 (0.01, 5.91)
IM TU 1000 mg/12 wk		0.48 (0.01, 13.15)	0.47 (0.01, 10.81)
IM TE 150 mg/2wk		0.78 (0.05, 12.46)	0.76 (0.06, 9.03)
IM TE 200 mg/2wk		4.59 (0.42, 61.23)	4.57 (0.45, 58.45)
IM TE 250 mg/4wk		0.92 (0.02, 38.30)	0.97 (0.02, 36.38)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.20 (0.00, 6.92)	0.21 (0.00, 5.26)
IM TU 1000 mg/12 wk		0.32 (0.00, 10.33)	0.32 (0.01, 9.33)
IM TE 150 mg/2wk		0.53 (0.03, 9.84)	0.53 (0.04, 8.33)
IM TE 200 mg/2wk		3.13 (0.23, 53.26)	3.21 (0.28, 48.88)
IM TE 250 mg/4wk		0.64 (0.01, 31.74)	0.68 (0.01, 31.57)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.54 (0.02, 121.90)	1.58 (0.02, 110.70)
IM TE 150 mg/2wk		2.63 (0.09, 132.80)	2.56 (0.12, 110.90)
IM TE 200 mg/2wk		15.33 (0.57, 932.00)	15.77 (0.76, 766.40)
IM TE 250 mg/4wk		3.14 (0.03, 353.00)	3.34 (0.04, 317.70)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	1.68 (0.05, 103.80)	1.64 (0.06, 82.68)
IM TE 200 mg/2wk		9.85 (0.33, 722.30)	10.14 (0.40, 532.10)
IM TE 250 mg/4wk		1.99 (0.02, 244.70)	2.14 (0.02, 230.20)

IM TE 200 mg/2wk	IM TE 150 mg/2wk	5.92 (0.37, 99.96)	6.11 (0.49, 93.50)
IM TE 250 mg/4wk		1.16 (0.02, 57.94)	1.29 (0.02, 52.05)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.20 (0.00, 8.57)	0.21 (0.00, 8.41)
Residual Deviance		291.7 (24 points)	19.64 (24 points)
DIC		83.828	83.40

Prostate cancer, continuity correction, treatments with zero arms dropped: Odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	2.88 (0.42, 20.23)	2.73 (0.43, 17.54)
Gel 5 mg/d		0.64 (0.03, 9.38)	0.63 (0.04, 8.01)
Gel 1% 50 mg/d		0.58 (0.08, 2.85)	0.56 (0.09, 2.55)
Gel 1% 100 mg/d		0.82 (0.08, 5.36)	0.81 (0.10, 5.12)
IM TE 150 mg/2wk		0.43 (0.05, 2.97)	0.42 (0.06, 2.35)
IM TE 200 mg/2wk		2.73 (0.38, 21.45)	2.55 (0.42, 18.58)
Gel 5 mg/d	Patch 5 mg/d	0.22 (0.01, 6.53)	0.22 (0.01, 5.26)
Gel 1% 50 mg/d		0.20 (0.01, 2.13)	0.20 (0.02, 1.83)
Gel 1% 100 mg/d		0.29 (0.02, 3.04)	0.30 (0.02, 2.73)
IM TE 150 mg/2wk		0.15 (0.01, 2.30)	0.15 (0.01, 1.91)
IM TE 200 mg/2wk		0.94 (0.12, 7.25)	0.95 (0.14, 6.49)
Gel 1% 50 mg/d	Gel 5 mg/d	0.91 (0.03, 25.01)	0.89 (0.04, 22.61)
Gel 1% 100 mg/d		1.27 (0.04, 38.86)	1.28 (0.05, 39.04)
IM TE 150 mg/2wk		0.67 (0.02, 22.28)	0.66 (0.03, 19.06)
IM TE 200 mg/2wk		4.26 (0.15, 164.00)	4.22 (0.18, 127.30)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.43 (0.10, 19.81)	1.45 (0.12, 16.92)
IM TE 150 mg/2wk		0.76 (0.05, 10.93)	0.75 (0.06, 9.05)
IM TE 200 mg/2wk		4.89 (0.37, 71.65)	4.66 (0.47, 59.71)
IM TE 150 mg/2wk	Gel 1% 100 mg/d	0.52 (0.03, 10.11)	0.52 (0.04, 7.97)
IM TE 200 mg/2wk		3.34 (0.25, 60.92)	3.24 (0.28, 48.05)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	6.25 (0.41, 125.90)	6.20 (0.49, 99.24)
DIC		15.19 (18 points)	15.36 (18 points)
Residual deviance		63.50	63.35

Serious adverse events, base case (no continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	1.14 (0.06, 15.71)	1.20 (0.07, 18.96)
Gel 1% 50 mg/d		1.35 (0.48, 3.86)	1.33 (0.57, 3.18)
Gel 1% 100 mg/d		1.35 (0.47, 3.41)	1.46 (0.69, 3.16)
Gel 1% 125 mg/d		2.57 (0.10, 98.48)	2.83 (0.09, 103.50)
Gel 1.62% 40.5 mg/d		0.74 (0.11, 7.32)	0.73 (0.13, 6.66)
Oral TU 160 mg/d		0.43 (0.10, 1.62)	0.44 (0.14, 1.26)
IM TU 1000 mg/9 wk		6.31 (0.06, 1541.00)	6.15 (0.06, 1119.00)

IM TU 1000 mg/12 wk		0.29 (0.06, 1.16)	0.30 (0.07, 1.03)
IM TE 250 mg/3 wk		1.49 (0.06, 24.34)	1.66 (0.08, 31.15)
Gel 1% 50 mg/d	Patch 5 mg/d	1.18 (0.07, 26.32)	1.12 (0.06, 21.79)
Gel 1% 100 mg/d		1.18 (0.07, 24.46)	1.22 (0.07, 23.85)
Gel 1% 125 mg/d		2.51 (0.04, 200.90)	2.43 (0.03, 212.90)
Gel 1.62% 40.5 mg/d		0.66 (0.03, 24.88)	0.64 (0.02, 21.61)
Oral TU 160 mg/d		0.38 (0.02, 9.17)	0.36 (0.02, 7.60)
IM TU 1000 mg/9 wk		5.33 (0.05, 1846.00)	4.81 (0.05, 1329.00)
IM TU 1000 mg/12 wk		0.25 (0.01, 7.01)	0.25 (0.01, 5.58)
IM TE 250 mg/3 wk		1.36 (0.23, 6.12)	1.44 (0.29, 5.24)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.00 (0.22, 3.95)	1.09 (0.35, 3.43)
Gel 1% 125 mg/d		1.90 (0.06, 80.61)	2.12 (0.06, 84.95)
Gel 1.62% 40.5 mg/d		0.56 (0.06, 6.53)	0.55 (0.08, 5.79)
Oral TU 160 mg/d		0.32 (0.05, 1.74)	0.33 (0.08, 1.27)
IM TU 1000 mg/9 wk		4.69 (0.04, 1207.00)	4.59 (0.04, 889.30)
IM TU 1000 mg/12 wk		0.21 (0.03, 1.23)	0.22 (0.04, 1.01)
IM TE 250 mg/3 wk		1.09 (0.04, 21.89)	1.24 (0.05, 25.92)
Gel 1% 125 mg/d	Gel 1% 100 mg/d	1.93 (0.07, 84.36)	1.93 (0.06, 75.77)
Gel 1.62% 40.5 mg/d		0.56 (0.07, 6.86)	0.51 (0.07, 5.13)
Oral TU 160 mg/d		0.32 (0.06, 1.74)	0.30 (0.07, 1.10)
IM TU 1000 mg/9 wk		4.76 (0.04, 1221.00)	4.19 (0.04, 811.50)
IM TU 1000 mg/12 wk		0.21 (0.03, 1.24)	0.21 (0.04, 0.87)
IM TE 250 mg/3 wk		1.10 (0.04, 22.14)	1.13 (0.05, 23.59)
Gel 1.62% 40.5 mg/d	Gel 1% 125 mg/d	0.30 (0.00, 16.80)	0.27 (0.00, 14.85)
Oral TU 160 mg/d		0.17 (0.00, 5.59)	0.15 (0.00, 5.31)
IM TU 1000 mg/9 wk		2.44 (0.01, 1316.00)	2.20 (0.01, 1104.00)
IM TU 1000 mg/12 wk		0.11 (0.00, 3.52)	0.11 (0.00, 4.04)
IM TE 250 mg/3 wk		0.52 (0.00, 38.90)	0.57 (0.01, 50.72)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.57 (0.04, 5.62)	0.58 (0.05, 4.57)
IM TU 1000 mg/9 wk		8.02 (0.04, 2338.00)	7.91 (0.05, 1981.00)
IM TU 1000 mg/12 wk		0.38 (0.02, 4.08)	0.40 (0.03, 3.43)
IM TE 250 mg/3 wk		1.92 (0.04, 54.23)	2.17 (0.06, 66.56)
IM TU 1000 mg/9 wk	Oral TU 160 mg/d	15.33 (0.12, 4135.00)	14.25 (0.13, 2924.00)
IM TU 1000 mg/12 wk		0.67 (0.09, 4.84)	0.69 (0.11, 3.75)
IM TE 250 mg/3 wk		3.48 (0.11, 79.25)	3.86 (0.16, 87.75)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.04 (0.00, 6.42)	0.05 (0.00, 5.56)
IM TE 250 mg/3 wk		0.24 (0.00, 23.82)	0.29 (0.00, 25.49)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	5.37 (0.16, 128.60)	5.63 (0.21, 144.20)
Residual Deviance		23.15 (27 points)	23.52 (27 points)
DIC		105.00	104.76

Serious adverse events, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	1.17 (0.11, 16.03)	1.32 (0.12, 14.09)
Gel 1% 50 mg/d		1.34 (0.49, 3.73)	1.34 (0.58, 3.18)
Gel 1% 100 mg/d		1.35 (0.48, 3.47)	1.47 (0.69, 3.15)

Gel 1% 125 mg/d		2.13 (0.12, 45.14)	2.19 (0.13, 43.18)
Gel 1.62% 40.5 mg/d		0.73 (0.11, 7.62)	0.75 (0.13, 6.85)
Oral TU 160 mg/d		0.45 (0.11, 1.55)	0.44 (0.14, 1.23)
IM TU 1000 mg/9 wk		2.90 (0.06, 201.30)	2.90 (0.07, 159.30)
IM TU 1000 mg/12 wk		0.34 (0.08, 1.22)	0.34 (0.09, 1.10)
IM TE 250 mg/3 wk		1.65 (0.11, 27.15)	1.89 (0.14, 24.54)
Gel 1% 50 mg/d	Patch 5 mg/d	1.14 (0.07, 14.84)	1.02 (0.08, 12.24)
Gel 1% 100 mg/d		1.14 (0.07, 14.58)	1.12 (0.09, 13.18)
Gel 1% 125 mg/d		1.77 (0.04, 87.70)	1.67 (0.04, 72.64)
Gel 1.62% 40.5 mg/d		0.63 (0.03, 17.52)	0.59 (0.03, 14.10)
Oral TU 160 mg/d		0.38 (0.02, 5.50)	0.33 (0.02, 4.44)
IM TU 1000 mg/9 wk		2.32 (0.06, 162.40)	2.14 (0.07, 109.80)
IM TU 1000 mg/12 wk		0.28 (0.02, 4.24)	0.25 (0.02, 3.58)
IM TE 250 mg/3 wk		1.44 (0.25, 6.18)	1.48 (0.31, 5.29)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.00 (0.23, 3.96)	1.10 (0.35, 3.39)
Gel 1% 125 mg/d		1.58 (0.08, 39.40)	1.63 (0.09, 35.39)
Gel 1.62% 40.5 mg/d		0.55 (0.06, 6.95)	0.56 (0.08, 5.92)
Oral TU 160 mg/d		0.33 (0.06, 1.63)	0.33 (0.08, 1.24)
IM TU 1000 mg/9 wk		2.16 (0.04, 170.20)	2.16 (0.05, 128.60)
IM TU 1000 mg/12 wk		0.25 (0.04, 1.28)	0.25 (0.05, 1.08)
IM TE 250 mg/3 wk		1.23 (0.07, 24.17)	1.41 (0.09, 20.66)
Gel 1% 125 mg/d	Gel 1% 100 mg/d	1.61 (0.08, 40.83)	1.49 (0.08, 31.80)
Gel 1.62% 40.5 mg/d		0.56 (0.07, 7.01)	0.51 (0.08, 5.32)
Oral TU 160 mg/d		0.33 (0.07, 1.73)	0.30 (0.08, 1.09)
IM TU 1000 mg/9 wk		2.18 (0.04, 176.80)	1.97 (0.04, 116.40)
IM TU 1000 mg/12 wk		0.25 (0.05, 1.33)	0.23 (0.05, 0.95)
IM TE 250 mg/3 wk		1.22 (0.07, 24.72)	1.28 (0.09, 18.44)
Gel 1.62% 40.5 mg/d	Gel 1% 125 mg/d	0.36 (0.01, 12.90)	0.35 (0.01, 12.39)
Oral TU 160 mg/d		0.21 (0.01, 4.72)	0.20 (0.01, 3.99)
IM TU 1000 mg/9 wk		1.35 (0.01, 241.90)	1.34 (0.01, 171.70)
IM TU 1000 mg/12 wk		0.16 (0.01, 3.51)	0.15 (0.01, 3.33)
IM TE 250 mg/3 wk		0.78 (0.01, 42.05)	0.85 (0.02, 37.85)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.61 (0.04, 5.42)	0.58 (0.05, 4.47)
IM TU 1000 mg/9 wk		3.76 (0.04, 416.40)	3.74 (0.05, 291.20)
IM TU 1000 mg/12 wk		0.45 (0.03, 4.73)	0.44 (0.03, 3.74)
IM TE 250 mg/3 wk		2.22 (0.06, 68.10)	2.43 (0.08, 56.71)
IM TU 1000 mg/9 wk	Oral TU 160 mg/d	6.70 (0.11, 549.70)	6.65 (0.14, 420.80)
IM TU 1000 mg/12 wk		0.76 (0.12, 4.68)	0.77 (0.15, 3.89)
IM TE 250 mg/3 wk		3.74 (0.19, 82.25)	4.32 (0.27, 71.72)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.12 (0.00, 6.24)	0.11 (0.00, 5.77)
IM TE 250 mg/3 wk		0.62 (0.01, 17.18)	0.68 (0.01, 17.73)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	5.08 (0.26, 108.80)	5.65 (0.32, 102.10)
Residual Deviance		23.16 (27 points)	23.29 (27 points)
DIC		115.72	114.99

Withdrawals due to adverse events, base case (no continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Patch 5 mg/d	Placebo	2.71 (0.69, 9.34)	3.07 (1.08, 9.38)*
Gel 1% 5 mg/d		0.83 (0.28, 2.81)	0.79 (0.39, 1.58)
Gel 1% 50 mg/d		0.85 (0.38, 1.65)	0.89 (0.53, 1.50)
Gel 1% 75 mg/d		3.61 (0.42, 40.86)	3.57 (0.52, 35.80)
Gel 1%, 100 mg/wk		0.78 (0.27, 1.91)	0.83 (0.42, 1.62)
Gel 1.62% 40.5 mg/d		9.83 (1.08, 193.30)*	9.86 (1.55, 187.30)*
Gel 2% 60 mg/d		1.61 (0.45, 5.80)	1.64 (0.76, 3.64)
Oral TU 120 mg/d		0.21 (0.00, 14.06)	0.22 (0.00, 15.73)
Oral TU 160 mg/d		1.01 (0.33, 3.39)	0.97 (0.43, 2.17)
Oral TU 120-160 mg/d		0.21 (0.00, 11.24)	0.19 (0.00, 12.24)
IM TU 1000 mg/9 wk		9.07 (0.08, 1830.00)	9.72 (0.11, 1457.00)
IM TU 1000 mg/12 wk		0.37 (0.12, 1.09)	0.38 (0.13, 0.98)
IM TE 100 mg/wk		0.19 (0.00, 17.08)	0.21 (0.00, 16.13)
IM TE 125 mg/wk		6.20 (0.76, 60.80)	6.35 (0.99, 60.31)
IM TE 150 mg/2 wk		0.72 (0.04, 12.02)	0.74 (0.04, 9.95)
IM TE 200 mg/2wk		2.59 (0.59, 12.46)	2.72 (0.72, 11.12)
IM TE 250 mg/3wk		3.99 (0.36, 69.56)	4.35 (0.47, 62.66)
IM TE 250 mg/4 wk		1.56 (0.12, 18.91)	1.59 (0.16, 17.61)
IM TE 300 mg/3wk		0.69 (0.10, 4.69)	0.68 (0.12, 3.24)
IM TE 50-400 mg/wk		0.26 (0.00, 22.45)	0.22 (0.00, 19.16)
IM TC 200 mg/2 wk		4.24 (0.54, 49.04)	4.65 (0.74, 45.36)
Gel 1% 5 mg/d	Patch 5 mg/d	0.31 (0.06, 2.05)	0.26 (0.07, 0.90)
Gel 1% 50 mg/d		0.31 (0.09, 1.20)	0.29 (0.09, 0.85)
Gel 1% 75 mg/d		1.37 (0.12, 21.00)	1.17 (0.12, 14.36)
Gel 1%, 100 mg/wk		0.29 (0.07, 1.20)	0.27 (0.08, 0.81)
Gel 1.62% 40.5 mg/d		3.77 (0.29, 91.94)	3.26 (0.36, 70.85)
Gel 2% 60 mg/d		0.59 (0.11, 4.11)	0.53 (0.14, 1.99)
Oral TU 120 mg/d		0.08 (0.00, 6.73)	0.07 (0.00, 5.71)
Oral TU 160 mg/d		0.37 (0.07, 2.40)	0.32 (0.08, 1.19)
Oral TU 120-160 mg/d		0.08 (0.00, 5.29)	0.06 (0.00, 4.57)
IM TU 1000 mg/9 wk		3.42 (0.03, 834.50)	3.11 (0.03, 536.20)
IM TU 1000 mg/12 wk		0.14 (0.03, 0.78)	0.12 (0.03, 0.51)
IM TE 100 mg/wk		0.07 (0.00, 8.27)	0.07 (0.00, 5.98)
IM TE 125 mg/wk		2.34 (0.21, 33.67)	2.07 (0.24, 24.50)
IM TE 150 mg/2 wk		0.27 (0.01, 6.13)	0.24 (0.01, 3.93)
IM TE 200 mg/2wk		0.97 (0.16, 6.48)	0.89 (0.17, 4.60)
IM TE 250 mg/3wk		1.52 (0.10, 34.89)	1.43 (0.12, 24.75)
IM TE 250 mg/4 wk		0.59 (0.03, 9.71)	0.52 (0.04, 7.21)
IM TE 300 mg/3wk		0.26 (0.03, 2.76)	0.22 (0.03, 1.48)
IM TE 50-400 mg/wk		0.10 (0.00, 9.92)	0.07 (0.00, 7.41)
IM TC 200 mg/2 wk		1.60 (0.14, 26.24)	1.53 (0.17, 18.95)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.02 (0.23, 3.58)	1.13 (0.48, 2.69)
Gel 1% 75 mg/d		4.31 (0.37, 60.78)	4.53 (0.58, 50.33)
Gel 1%, 100 mg/wk		0.94 (0.18, 3.70)	1.05 (0.40, 2.71)
Gel 1.62% 40.5 mg/d		11.96 (0.96, 276.10)	12.64 (1.72, 249.80)
Gel 2% 60 mg/d		1.95 (0.32, 10.28)	2.08 (0.74, 5.89)

Oral TU 120 mg/d	0.25 (0.00, 18.26)	0.27 (0.00, 20.62)
Oral TU 160 mg/d	1.22 (0.24, 6.15)	1.22 (0.42, 3.53)
Oral TU 120-160 mg/d	0.25 (0.00, 15.29)	0.24 (0.00, 15.98)
IM TU 1000 mg/9 wk	11.01 (0.08, 2415.00)	12.23 (0.13, 1909.00)
IM TU 1000 mg/12 wk	0.44 (0.08, 2.09)	0.47 (0.14, 1.54)
IM TE 100 mg/wk	0.23 (0.00, 23.01)	0.26 (0.00, 21.63)
IM TE 125 mg/wk	7.51 (0.65, 90.95)	8.06 (1.10, 85.55)
IM TE 150 mg/2 wk	0.86 (0.03, 17.29)	0.94 (0.05, 13.71)
IM TE 200 mg/2wk	3.13 (0.45, 20.84)	3.45 (0.77, 16.41)
IM TE 250 mg/3wk	4.87 (0.33, 106.70)	5.53 (0.54, 88.50)
IM TE 250 mg/4 wk	1.87 (0.12, 28.50)	2.01 (0.19, 24.47)
IM TE 300 mg/3wk	0.83 (0.09, 7.36)	0.85 (0.14, 4.76)
IM TE 50-400 mg/wk	0.30 (0.00, 30.85)	0.28 (0.00, 26.50)
IM TC 200 mg/2 wk	5.13 (0.46, 71.98)	5.91 (0.81, 64.22)
Gel 1% 75 mg/d Gel 1% 50 mg/d	4.31 (0.46, 56.28)	4.00 (0.54, 43.40)
Gel 1%, 100 mg/wk	0.92 (0.29, 2.86)	0.93 (0.41, 2.10)
Gel 1.62% 40.5 mg/d	11.78 (1.19, 248.70)	11.06 (1.59, 221.00)
Gel 2% 60 mg/d	1.90 (0.48, 8.88)	1.84 (0.73, 4.79)
Oral TU 120 mg/d	0.25 (0.00, 17.70)	0.24 (0.00, 18.22)
Oral TU 160 mg/d	1.20 (0.33, 5.32)	1.09 (0.41, 2.85)
Oral TU 120-160 mg/d	0.25 (0.00, 14.86)	0.21 (0.00, 14.02)
IM TU 1000 mg/9 wk	10.83 (0.09, 2289.00)	10.92 (0.12, 1687.00)
IM TU 1000 mg/12 wk	0.44 (0.11, 1.67)	0.42 (0.13, 1.27)
IM TE 100 mg/wk	0.23 (0.00, 22.83)	0.23 (0.00, 18.71)
IM TE 125 mg/wk	7.41 (0.83, 80.81)	7.15 (1.02, 71.83)
IM TE 150 mg/2 wk	0.86 (0.04, 15.80)	0.83 (0.04, 11.76)
IM TE 200 mg/2wk	3.08 (0.62, 17.25)	3.05 (0.74, 13.55)
IM TE 250 mg/3wk	4.81 (0.40, 95.06)	4.93 (0.50, 74.42)
IM TE 250 mg/4 wk	1.86 (0.13, 25.07)	1.78 (0.17, 21.01)
IM TE 300 mg/3wk	0.82 (0.11, 6.63)	0.76 (0.13, 3.97)
IM TE 50-400 mg/wk	0.31 (0.00, 28.23)	0.25 (0.00, 22.16)
IM TC 200 mg/2 wk	5.05 (0.58, 68.06)	5.23 (0.76, 53.16)
Gel 1%, 100 mg/wk Gel 1% 75 mg/d	0.21 (0.02, 2.22)	0.23 (0.02, 1.82)
Gel 1.62% 40.5 mg/d	2.87 (0.10, 109.00)	2.83 (0.14, 85.45)
Gel 2% 60 mg/d	0.44 (0.03, 5.45)	0.46 (0.04, 3.69)
Oral TU 120 mg/d	0.05 (0.00, 6.81)	0.06 (0.00, 6.80)
Oral TU 160 mg/d	0.28 (0.02, 3.42)	0.27 (0.02, 2.17)
Oral TU 120-160 mg/d	0.05 (0.00, 5.58)	0.05 (0.00, 5.34)
IM TU 1000 mg/9 wk	2.45 (0.01, 683.80)	2.63 (0.02, 586.30)
IM TU 1000 mg/12 wk	0.10 (0.01, 1.17)	0.10 (0.01, 0.90)
IM TE 100 mg/wk	0.05 (0.00, 7.82)	0.05 (0.00, 7.10)
IM TE 125 mg/wk	1.72 (0.07, 41.05)	1.76 (0.10, 32.68)
IM TE 150 mg/2 wk	0.20 (0.00, 6.59)	0.20 (0.01, 5.17)
IM TE 200 mg/2wk	0.72 (0.04, 10.37)	0.75 (0.05, 8.20)
IM TE 250 mg/3wk	1.15 (0.03, 39.95)	1.21 (0.05, 32.66)
IM TE 250 mg/4 wk	0.42 (0.01, 11.85)	0.43 (0.02, 9.86)
IM TE 300 mg/3wk	0.19 (0.01, 3.53)	0.18 (0.01, 2.29)
IM TE 50-400 mg/wk	0.07 (0.00, 10.28)	0.06 (0.00, 8.24)
IM TC 200 mg/2 wk	1.19 (0.05, 32.88)	1.30 (0.07, 24.86)
Gel 1.62% 40.5 mg/d Gel 1%, 100 mg/wk	12.78 (1.18, 293.00)	11.98 (1.62, 238.40)

Gel 2% 60 mg/d	2.07 (0.45, 11.27)	1.97 (0.72, 5.64)
Oral TU 120 mg/d	0.27 (0.00, 20.85)	0.26 (0.00, 19.58)
Oral TU 160 mg/d	1.31 (0.31, 6.72)	1.17 (0.41, 3.34)
Oral TU 120-160 mg/d	0.26 (0.00, 16.89)	0.23 (0.00, 15.54)
IM TU 1000 mg/9 wk	11.66 (0.10, 2556.00)	11.69 (0.12, 1832.00)
IM TU 1000 mg/12 wk	0.47 (0.11, 2.14)	0.45 (0.13, 1.47)
IM TE 100 mg/wk	0.25 (0.00, 25.53)	0.25 (0.00, 20.47)
IM TE 125 mg/wk	7.96 (0.83, 100.30)	7.70 (1.05, 80.62)
IM TE 150 mg/2 wk	0.93 (0.04, 19.39)	0.89 (0.04, 13.18)
IM TE 200 mg/2wk	3.37 (0.61, 21.55)	3.29 (0.75, 15.48)
IM TE 250 mg/3wk	5.31 (0.41, 107.60)	5.29 (0.51, 83.49)
IM TE 250 mg/4 wk	2.02 (0.14, 30.25)	1.91 (0.18, 23.74)
IM TE 300 mg/3wk	0.89 (0.11, 8.03)	0.81 (0.13, 4.52)
IM TE 50-400 mg/wk	0.33 (0.00, 33.32)	0.27 (0.00, 24.79)
IM TC 200 mg/2 wk	5.52 (0.58, 79.53)	5.64 (0.77, 60.72)
Gel 2% 60 mg/d Gel 1.62% 40.5 mg/d	0.16 (0.01, 2.09)	0.16 (0.01, 1.28)
Oral TU 120 mg/d	0.02 (0.00, 2.44)	0.02 (0.00, 2.39)
Oral TU 160 mg/d	0.10 (0.00, 1.36)	0.10 (0.00, 0.74)
Oral TU 120-160 mg/d	0.02 (0.00, 2.09)	0.02 (0.00, 1.95)
IM TU 1000 mg/9 wk	0.89 (0.00, 281.70)	0.90 (0.00, 199.60)
IM TU 1000 mg/12 wk	0.04 (0.00, 0.45)	0.04 (0.00, 0.32)
IM TE 100 mg/wk	0.02 (0.00, 2.67)	0.02 (0.00, 2.45)
IM TE 125 mg/wk	0.61 (0.02, 15.31)	0.63 (0.02, 11.85)
IM TE 150 mg/2 wk	0.07 (0.00, 2.87)	0.07 (0.00, 1.90)
IM TE 200 mg/2wk	0.26 (0.01, 3.90)	0.27 (0.01, 2.88)
IM TE 250 mg/3wk	0.39 (0.01, 16.12)	0.43 (0.01, 11.89)
IM TE 250 mg/4 wk	0.15 (0.00, 4.43)	0.15 (0.00, 3.56)
IM TE 300 mg/3wk	0.07 (0.00, 1.32)	0.07 (0.00, 0.82)
IM TE 50-400 mg/wk	0.02 (0.00, 4.15)	0.02 (0.00, 2.97)
IM TC 200 mg/2 wk	0.43 (0.01, 10.74)	0.46 (0.02, 8.85)
Oral TU 120 mg/d Gel 2% 60 mg/d	0.13 (0.00, 10.58)	0.13 (0.00, 10.17)
Oral TU 160 mg/d	0.63 (0.11, 3.63)	0.59 (0.19, 1.81)
Oral TU 120-160 mg/d	0.13 (0.00, 8.41)	0.12 (0.00, 7.93)
IM TU 1000 mg/9 wk	5.69 (0.04, 1336.00)	5.93 (0.06, 934.00)
IM TU 1000 mg/12 wk	0.23 (0.04, 1.22)	0.23 (0.06, 0.79)
IM TE 100 mg/wk	0.12 (0.00, 12.83)	0.13 (0.00, 10.52)
IM TE 125 mg/wk	3.88 (0.33, 52.80)	3.90 (0.51, 41.08)
IM TE 150 mg/2 wk	0.44 (0.02, 9.70)	0.45 (0.02, 6.73)
IM TE 200 mg/2wk	1.61 (0.23, 11.98)	1.66 (0.35, 8.22)
IM TE 250 mg/3wk	2.49 (0.16, 56.55)	2.67 (0.25, 43.55)
IM TE 250 mg/4 wk	0.96 (0.06, 16.20)	0.97 (0.09, 12.06)
IM TE 300 mg/3wk	0.43 (0.04, 4.22)	0.41 (0.06, 2.37)
IM TE 50-400 mg/wk	0.16 (0.00, 16.98)	0.13 (0.00, 13.03)
IM TC 200 mg/2 wk	2.61 (0.24, 41.97)	2.85 (0.37, 31.51)
Oral TU 160 mg/d Oral TU 120 mg/d	4.80 (0.06, 1175.00)	4.50 (0.06, 972.00)
Oral TU 120-160 mg/d	1.01 (0.00, 725.30)	0.86 (0.00, 708.70)
IM TU 1000 mg/9 wk	50.07 (0.08, 59760.00)	50.83 (0.09, 60890.00)
IM TU 1000 mg/12 wk	1.73 (0.02, 441.40)	1.73 (0.02, 385.70)
IM TE 100 mg/wk	0.99 (0.00, 685.90)	0.99 (0.00, 911.00)
IM TE 125 mg/wk	30.25 (0.29, 10200.00)	31.89 (0.26, 9073.00)

IM TE 150 mg/2 wk		3.66 (0.02, 1450.00)	3.45 (0.02, 1257.00)
IM TE 200 mg/2wk		12.62 (0.16, 3147.00)	12.92 (0.14, 3089.00)
IM TE 250 mg/3wk		20.98 (0.17, 7124.00)	22.00 (0.17, 7457.00)
IM TE 250 mg/4 wk		7.52 (0.06, 2801.00)	7.71 (0.06, 2442.00)
IM TE 300 mg/3wk		3.30 (0.03, 1012.00)	3.15 (0.03, 796.10)
IM TE 50-400 mg/wk		1.33 (0.00, 867.40)	1.06 (0.00, 1068.00)
IM TC 200 mg/2 wk		21.67 (0.19, 8290.00)	23.25 (0.20, 6870.00)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.20 (0.00, 13.52)	0.20 (0.00, 13.45)
IM TU 1000 mg/9 wk		8.71 (0.07, 1877.00)	9.99 (0.10, 1609.00)
IM TU 1000 mg/12 wk		0.36 (0.07, 1.79)	0.39 (0.10, 1.37)
IM TE 100 mg/wk		0.19 (0.00, 19.77)	0.21 (0.00, 17.98)
IM TE 125 mg/wk		6.15 (0.53, 80.78)	6.65 (0.87, 71.52)
IM TE 150 mg/2 wk		0.72 (0.03, 14.20)	0.77 (0.04, 11.79)
IM TE 200 mg/2wk		2.57 (0.37, 16.98)	2.81 (0.59, 14.12)
IM TE 250 mg/3wk		4.01 (0.27, 86.72)	4.54 (0.42, 73.42)
IM TE 250 mg/4 wk		1.53 (0.09, 24.23)	1.64 (0.15, 21.35)
IM TE 300 mg/3wk		0.67 (0.07, 6.25)	0.69 (0.11, 4.07)
IM TE 50-400 mg/wk		0.25 (0.00, 24.81)	0.23 (0.00, 22.08)
IM TC 200 mg/2 wk		4.21 (0.37, 62.76)	4.81 (0.64, 53.72)
IM TU 1000 mg/9 wk	Oral TU 120-160 mg/d	54.11 (0.09, 63000.00)	57.96 (0.10, 64010.00)
IM TU 1000 mg/12 wk		1.80 (0.03, 402.00)	1.98 (0.03, 398.80)
IM TE 100 mg/wk		1.01 (0.00, 1841.00)	1.10 (0.00, 941.60)
IM TE 125 mg/wk		31.97 (0.28, 10330.00)	35.94 (0.34, 9326.00)
IM TE 150 mg/2 wk		3.82 (0.02, 1518.00)	3.98 (0.02, 1256.00)
IM TE 200 mg/2wk		12.84 (0.17, 3321.00)	14.66 (0.18, 3216.00)
IM TE 250 mg/3wk		21.69 (0.19, 10280.00)	25.13 (0.20, 7699.00)
IM TE 250 mg/4 wk		8.27 (0.06, 2768.00)	8.72 (0.07, 2506.00)
IM TE 300 mg/3wk		3.51 (0.04, 988.70)	3.58 (0.04, 819.30)
IM TE 50-400 mg/wk		1.39 (0.00, 1434.00)	1.22 (0.00, 1050.00)
IM TC 200 mg/2 wk		23.29 (0.22, 6149.00)	26.83 (0.25, 6950.00)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.04 (0.00, 4.74)	0.04 (0.00, 3.76)
IM TE 100 mg/wk		0.02 (0.00, 12.26)	0.02 (0.00, 11.31)
IM TE 125 mg/wk		0.68 (0.00, 124.00)	0.68 (0.00, 95.48)
IM TE 150 mg/2 wk		0.08 (0.00, 17.88)	0.07 (0.00, 13.37)
IM TE 200 mg/2wk		0.28 (0.00, 42.36)	0.28 (0.00, 29.69)
IM TE 250 mg/3wk		0.48 (0.00, 50.85)	0.50 (0.00, 40.81)
IM TE 250 mg/4 wk		0.17 (0.00, 32.54)	0.16 (0.00, 26.39)
IM TE 300 mg/3wk		0.08 (0.00, 11.77)	0.07 (0.00, 7.84)
IM TE 50-400 mg/wk		0.03 (0.00, 16.27)	0.02 (0.00, 13.55)
IM TC 200 mg/2 wk		0.47 (0.00, 84.82)	0.50 (0.00, 73.23)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	0.53 (0.00, 54.54)	0.55 (0.00, 48.90)
IM TE 125 mg/wk		17.10 (1.55, 222.00)	17.23 (2.05, 197.10)
IM TE 150 mg/2 wk		1.97 (0.08, 39.71)	1.99 (0.09, 32.27)
IM TE 200 mg/2wk		7.07 (1.15, 51.76)	7.29 (1.40, 41.46)
IM TE 250 mg/3wk		11.02 (0.78, 245.80)	11.85 (1.02, 201.80)
IM TE 250 mg/4 wk		4.27 (0.27, 64.61)	4.29 (0.36, 58.00)
IM TE 300 mg/3wk		1.86 (0.20, 17.12)	1.80 (0.26, 11.63)
IM TE 50-400 mg/wk		0.70 (0.00, 69.03)	0.59 (0.00, 58.90)
IM TC 200 mg/2 wk		11.88 (1.09, 163.80)	12.62 (1.53, 151.50)
IM TE 125 mg/wk	IM TE 100 mg/wk	35.32 (0.23, 12740.00)	32.90 (0.26, 8948.00)

IM TE 150 mg/2 wk		3.68 (0.02, 2014.00)	3.59 (0.02, 1171.00)
IM TE 200 mg/2wk		14.04 (0.11, 4764.00)	13.31 (0.14, 3057.00)
IM TE 250 mg/3wk		23.47 (0.14, 9643.00)	22.71 (0.15, 7063.00)
IM TE 250 mg/4 wk		8.71 (0.04, 3421.00)	7.99 (0.06, 2396.00)
IM TE 300 mg/3wk		3.69 (0.03, 1434.00)	3.29 (0.03, 762.30)
IM TE 50-400 mg/wk		1.47 (0.00, 1428.00)	1.07 (0.00, 1063.00)
IM TC 200 mg/2 wk		23.49 (0.14, 8580.00)	24.18 (0.19, 6681.00)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.11 (0.00, 3.73)	0.11 (0.00, 2.79)
IM TE 200 mg/2wk		0.41 (0.03, 5.91)	0.42 (0.03, 4.50)
IM TE 250 mg/3wk		0.66 (0.02, 22.82)	0.68 (0.03, 17.96)
IM TE 250 mg/4 wk		0.25 (0.01, 6.55)	0.25 (0.01, 5.25)
IM TE 300 mg/3wk		0.11 (0.01, 1.86)	0.10 (0.01, 1.20)
IM TE 50-400 mg/wk		0.04 (0.00, 5.46)	0.03 (0.00, 4.38)
IM TC 200 mg/2 wk		0.68 (0.03, 16.72)	0.73 (0.04, 13.68)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.63 (0.15, 106.90)	3.72 (0.20, 89.53)
IM TE 250 mg/3wk		5.65 (0.14, 356.30)	6.26 (0.19, 297.50)
IM TE 250 mg/4 wk		2.13 (0.05, 108.10)	2.21 (0.07, 91.28)
IM TE 300 mg/3wk		0.97 (0.03, 31.21)	0.91 (0.04, 24.72)
IM TE 50-400 mg/wk		0.37 (0.00, 70.08)	0.30 (0.00, 63.84)
IM TC 200 mg/2 wk		6.00 (0.19, 287.10)	6.55 (0.26, 256.30)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.58 (0.09, 35.45)	1.63 (0.11, 31.22)
IM TE 250 mg/4 wk		0.60 (0.03, 10.93)	0.58 (0.04, 9.15)
IM TE 300 mg/3wk		0.27 (0.02, 3.00)	0.25 (0.03, 1.96)
IM TE 50-400 mg/wk		0.10 (0.00, 11.11)	0.08 (0.00, 8.88)
IM TC 200 mg/2 wk		1.65 (0.13, 29.08)	1.72 (0.17, 23.82)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.38 (0.01, 11.94)	0.36 (0.01, 9.37)
IM TE 300 mg/3wk		0.17 (0.01, 3.93)	0.15 (0.01, 2.40)
IM TE 50-400 mg/wk		0.06 (0.00, 8.67)	0.05 (0.00, 7.84)
IM TC 200 mg/2 wk		1.08 (0.03, 31.66)	1.07 (0.04, 25.26)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.43 (0.02, 10.80)	0.42 (0.02, 6.63)
IM TE 50-400 mg/wk		0.16 (0.00, 24.32)	0.13 (0.00, 21.88)
IM TC 200 mg/2 wk		2.79 (0.11, 93.18)	2.98 (0.14, 70.20)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.36 (0.00, 51.90)	0.33 (0.00, 38.41)
IM TC 200 mg/2 wk		6.28 (0.35, 141.70)	7.12 (0.61, 114.90)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	17.41 (0.13, 5180.00)	22.61 (0.16, 7004.00)
Residual deviance		85.69 (81 points)	90.21 (81 points)
DIC		290.86	291.98

Withdrawals due to adverse events, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
Patch 5 mg/d	Placebo	2.38 (0.79, 7.32)	2.62 (0.99, 7.07)
Gel 1% 5 mg/d		0.83 (0.32, 2.29)	0.80 (0.40, 1.58)
Gel 1% 50 mg/d		0.88 (0.46, 1.63)	0.90 (0.54, 1.49)
Gel 1% 75 mg/d		3.51 (0.44, 41.31)	3.59 (0.53, 34.44)
Gel 1%, 100 mg/wk		0.80 (0.32, 1.82)	0.82 (0.42, 1.58)
Gel 1.62% 40.5 mg/d		9.51 (1.26, 155.90)	9.53 (1.54, 140.40)

Gel 2% 60 mg/d		1.64 (0.53, 5.08)	1.64 (0.75, 3.61)
Oral TU 120 mg/d		0.61 (0.01, 15.56)	0.56 (0.01, 13.22)
Oral TU 160 mg/d		1.02 (0.38, 2.89)	0.98 (0.45, 2.12)
Oral TU 120-160 mg/d		0.52 (0.01, 12.16)	0.49 (0.01, 10.39)
IM TU 1000 mg/9 wk		4.69 (0.12, 254.20)	4.58 (0.13, 214.30)
IM TU 1000 mg/12 wk		0.45 (0.16, 1.16)	0.44 (0.17, 1.07)
IM TE 100 mg/wk		0.55 (0.01, 12.87)	0.57 (0.01, 14.60)
IM TE 125 mg/wk		6.16 (0.84, 55.57)	6.38 (0.99, 59.19)
IM TE 150 mg/2 wk		0.73 (0.04, 9.95)	0.74 (0.04, 9.78)
IM TE 200 mg/2wk		2.38 (0.67, 9.40)	2.50 (0.75, 8.93)
IM TE 250 mg/3wk		3.27 (0.42, 37.44)	3.47 (0.49, 35.88)
IM TE 250 mg/4 wk		1.48 (0.14, 16.80)	1.55 (0.16, 16.69)
IM TE 300 mg/3wk		0.69 (0.11, 3.92)	0.68 (0.13, 3.28)
IM TE 50-400 mg/wk		0.62 (0.02, 15.24)	0.62 (0.02, 18.31)
IM TC 200 mg/2 wk		4.46 (0.60, 45.09)	4.62 (0.72, 42.32)
Gel 1% 5 mg/d	Patch 5 mg/d	0.35 (0.08, 1.68)	0.30 (0.09, 1.00)
Gel 1% 50 mg/d		0.37 (0.11, 1.18)	0.34 (0.12, 0.93)
Gel 1% 75 mg/d		1.48 (0.15, 20.66)	1.39 (0.16, 15.90)
Gel 1%, 100 mg/wk		0.33 (0.10, 1.14)	0.32 (0.11, 0.88)
Gel 1.62% 40.5 mg/d		4.07 (0.40, 76.90)	3.73 (0.46, 63.29)
Gel 2% 60 mg/d		0.69 (0.14, 3.47)	0.62 (0.18, 2.21)
Oral TU 120 mg/d		0.25 (0.00, 8.13)	0.21 (0.00, 5.86)
Oral TU 160 mg/d		0.43 (0.10, 1.97)	0.37 (0.10, 1.28)
Oral TU 120-160 mg/d		0.22 (0.00, 6.34)	0.19 (0.00, 4.64)
IM TU 1000 mg/9 wk		1.92 (0.04, 121.10)	1.76 (0.04, 89.94)
IM TU 1000 mg/12 wk		0.18 (0.04, 0.81)	0.17 (0.04, 0.63)
IM TE 100 mg/wk		0.23 (0.01, 6.99)	0.22 (0.00, 6.53)
IM TE 125 mg/wk		2.58 (0.26, 31.05)	2.44 (0.29, 27.82)
IM TE 150 mg/2 wk		0.30 (0.01, 5.08)	0.28 (0.01, 4.54)
IM TE 200 mg/2wk		1.01 (0.22, 4.94)	0.95 (0.23, 4.09)
IM TE 250 mg/3wk		1.38 (0.14, 20.97)	1.33 (0.14, 16.69)
IM TE 250 mg/4 wk		0.64 (0.04, 9.09)	0.59 (0.05, 7.73)
IM TE 300 mg/3wk		0.29 (0.03, 2.27)	0.26 (0.04, 1.65)
IM TE 50-400 mg/wk		0.26 (0.01, 7.83)	0.24 (0.01, 7.95)
IM TC 200 mg/2 wk		1.87 (0.19, 25.42)	1.78 (0.21, 19.67)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.05 (0.31, 3.25)	1.12 (0.48, 2.65)
Gel 1% 75 mg/d		4.25 (0.41, 58.35)	4.51 (0.58, 47.42)
Gel 1%, 100 mg/wk		0.96 (0.24, 3.35)	1.03 (0.40, 2.66)
Gel 1.62% 40.5 mg/d		11.30 (1.17, 220.30)	12.04 (1.69, 190.90)
Gel 2% 60 mg/d		1.98 (0.43, 8.36)	2.04 (0.73, 5.87)
Oral TU 120 mg/d		0.73 (0.01, 20.42)	0.70 (0.01, 17.86)
Oral TU 160 mg/d		1.22 (0.30, 4.95)	1.23 (0.43, 3.43)
Oral TU 120-160 mg/d		0.61 (0.01, 17.44)	0.62 (0.01, 13.94)
IM TU 1000 mg/9 wk		5.50 (0.13, 336.30)	5.74 (0.15, 279.90)
IM TU 1000 mg/12 wk		0.53 (0.12, 2.07)	0.55 (0.17, 1.67)

IM TE 100 mg/wk		0.66 (0.02, 16.93)	0.72 (0.02, 19.87)
IM TE 125 mg/wk		7.41 (0.76, 80.35)	8.01 (1.11, 80.67)
IM TE 150 mg/2 wk		0.87 (0.04, 14.03)	0.92 (0.04, 13.41)
IM TE 200 mg/2wk		2.86 (0.57, 14.99)	3.13 (0.78, 13.28)
IM TE 250 mg/3wk		3.92 (0.40, 50.54)	4.35 (0.54, 49.51)
IM TE 250 mg/4 wk		1.78 (0.14, 23.57)	1.94 (0.19, 22.82)
IM TE 300 mg/3wk		0.83 (0.10, 5.93)	0.85 (0.14, 4.72)
IM TE 50-400 mg/wk		0.74 (0.02, 21.23)	0.77 (0.02, 24.52)
IM TC 200 mg/2 wk		5.40 (0.53, 64.88)	5.78 (0.79, 58.72)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	4.05 (0.47, 51.49)	4.01 (0.55, 40.66)
Gel 1%, 100 mg/wk		0.91 (0.32, 2.50)	0.92 (0.41, 2.02)
Gel 1.62% 40.5 mg/d		11.03 (1.23, 186.40)	10.68 (1.60, 161.60)
Gel 2% 60 mg/d		1.86 (0.53, 7.10)	1.82 (0.72, 4.68)
Oral TU 120 mg/d		0.70 (0.01, 19.06)	0.62 (0.01, 15.33)
Oral TU 160 mg/d		1.15 (0.37, 4.09)	1.10 (0.43, 2.74)
Oral TU 120-160 mg/d		0.59 (0.01, 15.01)	0.55 (0.01, 12.13)
IM TU 1000 mg/9 wk		5.34 (0.13, 307.90)	5.11 (0.14, 244.30)
IM TU 1000 mg/12 wk		0.50 (0.15, 1.63)	0.49 (0.16, 1.36)
IM TE 100 mg/wk		0.62 (0.02, 15.75)	0.64 (0.01, 16.73)
IM TE 125 mg/wk		7.03 (0.90, 70.40)	7.13 (1.02, 70.01)
IM TE 150 mg/2 wk		0.83 (0.04, 11.99)	0.82 (0.04, 11.50)
IM TE 200 mg/2wk		2.72 (0.68, 12.29)	2.78 (0.77, 10.62)
IM TE 250 mg/3wk		3.75 (0.44, 44.82)	3.87 (0.51, 42.63)
IM TE 250 mg/4 wk		1.70 (0.16, 20.89)	1.73 (0.17, 19.81)
IM TE 300 mg/3wk		0.79 (0.12, 5.05)	0.75 (0.13, 4.00)
IM TE 50-400 mg/wk		0.71 (0.02, 18.47)	0.69 (0.02, 21.25)
IM TC 200 mg/2 wk		5.13 (0.61, 58.82)	5.15 (0.74, 49.59)
Gel 1%, 100 mg/wk	Gel 1% 75 mg/d	0.22 (0.02, 2.15)	0.23 (0.02, 1.75)
Gel 1.62% 40.5 mg/d		2.68 (0.12, 92.05)	2.74 (0.14, 72.31)
Gel 2% 60 mg/d		0.46 (0.03, 5.21)	0.45 (0.04, 3.63)
Oral TU 120 mg/d		0.16 (0.00, 8.25)	0.15 (0.00, 6.35)
Oral TU 160 mg/d		0.29 (0.02, 3.05)	0.27 (0.02, 2.16)
Oral TU 120-160 mg/d		0.14 (0.00, 7.06)	0.13 (0.00, 5.07)
IM TU 1000 mg/9 wk		1.30 (0.02, 112.70)	1.23 (0.02, 93.49)
IM TU 1000 mg/12 wk		0.12 (0.01, 1.26)	0.12 (0.01, 1.02)
IM TE 100 mg/wk		0.14 (0.00, 7.27)	0.15 (0.00, 6.96)
IM TE 125 mg/wk		1.73 (0.07, 38.45)	1.77 (0.10, 32.58)
IM TE 150 mg/2 wk		0.19 (0.00, 6.20)	0.20 (0.01, 5.39)
IM TE 200 mg/2wk		0.67 (0.04, 8.76)	0.69 (0.05, 6.97)
IM TE 250 mg/3wk		0.93 (0.04, 22.08)	0.97 (0.05, 19.73)
IM TE 250 mg/4 wk		0.42 (0.01, 9.61)	0.43 (0.02, 9.08)
IM TE 300 mg/3wk		0.19 (0.01, 2.87)	0.19 (0.01, 2.26)
IM TE 50-400 mg/wk		0.17 (0.00, 7.91)	0.17 (0.00, 8.39)
IM TC 200 mg/2 wk		1.27 (0.05, 29.57)	1.28 (0.07, 23.35)
Gel 1.62% 40.5 mg/d	Gel 1%, 100 mg/wk	12.04 (1.35, 214.50)	11.78 (1.65, 184.10)

Gel 2% 60 mg/d		2.06 (0.53, 8.85)	1.99 (0.72, 5.57)
Oral TU 120 mg/d		0.78 (0.02, 21.32)	0.68 (0.01, 17.11)
Oral TU 160 mg/d		1.27 (0.37, 5.05)	1.19 (0.43, 3.28)
Oral TU 120-160 mg/d		0.65 (0.01, 17.79)	0.60 (0.01, 13.54)
IM TU 1000 mg/9 wk		5.99 (0.14, 341.80)	5.58 (0.15, 272.40)
IM TU 1000 mg/12 wk		0.56 (0.15, 2.10)	0.53 (0.17, 1.62)
IM TE 100 mg/wk		0.68 (0.02, 18.28)	0.70 (0.02, 18.66)
IM TE 125 mg/wk		7.80 (0.88, 85.90)	7.82 (1.07, 78.14)
IM TE 150 mg/2 wk		0.92 (0.04, 14.93)	0.89 (0.04, 12.85)
IM TE 200 mg/2wk		3.01 (0.68, 14.57)	3.03 (0.78, 12.41)
IM TE 250 mg/3wk		4.15 (0.44, 53.17)	4.21 (0.53, 47.53)
IM TE 250 mg/4 wk		1.89 (0.16, 24.96)	1.88 (0.18, 22.35)
IM TE 300 mg/3wk		0.86 (0.12, 6.10)	0.83 (0.14, 4.51)
IM TE 50-400 mg/wk		0.79 (0.02, 21.47)	0.76 (0.02, 23.39)
IM TC 200 mg/2 wk		5.64 (0.66, 68.34)	5.60 (0.78, 56.23)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.17 (0.01, 1.72)	0.17 (0.01, 1.27)
Oral TU 120 mg/d		0.06 (0.00, 3.07)	0.05 (0.00, 2.27)
Oral TU 160 mg/d		0.11 (0.01, 1.10)	0.10 (0.01, 0.77)
Oral TU 120-160 mg/d		0.05 (0.00, 2.82)	0.05 (0.00, 1.87)
IM TU 1000 mg/9 wk		0.46 (0.00, 48.30)	0.45 (0.01, 33.53)
IM TU 1000 mg/12 wk		0.05 (0.00, 0.45)	0.04 (0.00, 0.36)
IM TE 100 mg/wk		0.05 (0.00, 2.54)	0.05 (0.00, 2.58)
IM TE 125 mg/wk		0.62 (0.02, 13.10)	0.65 (0.03, 11.84)
IM TE 150 mg/2 wk		0.07 (0.00, 2.07)	0.07 (0.00, 1.87)
IM TE 200 mg/2wk		0.25 (0.01, 2.77)	0.25 (0.01, 2.50)
IM TE 250 mg/3wk		0.32 (0.01, 8.28)	0.35 (0.01, 7.19)
IM TE 250 mg/4 wk		0.15 (0.00, 3.47)	0.15 (0.00, 3.34)
IM TE 300 mg/3wk		0.07 (0.00, 1.04)	0.07 (0.00, 0.83)
IM TE 50-400 mg/wk		0.06 (0.00, 2.82)	0.06 (0.00, 3.21)
IM TC 200 mg/2 wk		0.46 (0.02, 9.80)	0.47 (0.02, 8.69)
Oral TU 120 mg/d	Gel 2% 60 mg/d	0.37 (0.01, 11.56)	0.34 (0.01, 8.81)
Oral TU 160 mg/d		0.61 (0.14, 2.90)	0.60 (0.20, 1.81)
Oral TU 120-160 mg/d		0.30 (0.01, 9.09)	0.30 (0.01, 6.93)
IM TU 1000 mg/9 wk		2.83 (0.06, 179.00)	2.81 (0.07, 141.60)
IM TU 1000 mg/12 wk		0.27 (0.06, 1.19)	0.27 (0.08, 0.88)
IM TE 100 mg/wk		0.33 (0.01, 9.38)	0.35 (0.01, 9.75)
IM TE 125 mg/wk		3.77 (0.37, 43.92)	3.94 (0.51, 40.75)
IM TE 150 mg/2 wk		0.44 (0.02, 7.65)	0.45 (0.02, 6.80)
IM TE 200 mg/2wk		1.46 (0.26, 8.36)	1.53 (0.36, 6.73)
IM TE 250 mg/3wk		2.01 (0.19, 27.19)	2.13 (0.25, 24.81)
IM TE 250 mg/4 wk		0.91 (0.07, 13.22)	0.95 (0.09, 11.82)
IM TE 300 mg/3wk		0.42 (0.05, 3.27)	0.41 (0.06, 2.41)
IM TE 50-400 mg/wk		0.37 (0.01, 11.52)	0.38 (0.01, 12.32)
IM TC 200 mg/2 wk		2.74 (0.27, 34.84)	2.84 (0.38, 29.59)
Oral TU 160 mg/d	Oral TU 120 mg/d	1.68 (0.06, 82.06)	1.77 (0.07, 83.62)

Oral TU 120-160 mg/d		0.82 (0.01, 122.60)	0.87 (0.01, 113.30)
IM TU 1000 mg/9 wk		7.63 (0.06, 2130.00)	8.74 (0.07, 1721.00)
IM TU 1000 mg/12 wk		0.72 (0.02, 41.46)	0.79 (0.03, 38.85)
IM TE 100 mg/wk		0.88 (0.01, 114.50)	1.04 (0.01, 141.80)
IM TE 125 mg/wk		10.44 (0.24, 761.50)	12.17 (0.29, 897.30)
IM TE 150 mg/2 wk		1.17 (0.01, 146.00)	1.33 (0.02, 130.20)
IM TE 200 mg/2wk		4.03 (0.12, 216.80)	4.54 (0.15, 237.80)
IM TE 250 mg/3wk		5.59 (0.13, 436.30)	6.60 (0.15, 519.40)
IM TE 250 mg/4 wk		2.46 (0.05, 224.70)	2.89 (0.06, 228.40)
IM TE 300 mg/3wk		1.11 (0.03, 78.38)	1.23 (0.03, 75.08)
IM TE 50-400 mg/wk		1.01 (0.01, 159.70)	1.14 (0.01, 169.60)
IM TC 200 mg/2 wk		7.37 (0.16, 648.90)	8.74 (0.21, 634.70)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.50 (0.01, 13.86)	0.50 (0.01, 11.69)
IM TU 1000 mg/9 wk		4.57 (0.10, 279.50)	4.64 (0.12, 231.90)
IM TU 1000 mg/12 wk		0.44 (0.10, 1.73)	0.44 (0.13, 1.45)
IM TE 100 mg/wk		0.54 (0.01, 14.39)	0.58 (0.01, 16.47)
IM TE 125 mg/wk		6.07 (0.63, 68.56)	6.54 (0.87, 69.19)
IM TE 150 mg/2 wk		0.71 (0.03, 11.55)	0.75 (0.03, 11.19)
IM TE 200 mg/2wk		2.35 (0.45, 12.54)	2.55 (0.60, 11.16)
IM TE 250 mg/3wk		3.23 (0.33, 42.24)	3.56 (0.42, 41.55)
IM TE 250 mg/4 wk		1.47 (0.12, 20.10)	1.58 (0.15, 19.70)
IM TE 300 mg/3wk		0.68 (0.08, 4.87)	0.69 (0.11, 3.98)
IM TE 50-400 mg/wk		0.60 (0.02, 17.98)	0.63 (0.01, 20.40)
IM TC 200 mg/2 wk		4.40 (0.46, 52.83)	4.74 (0.62, 47.99)
IM TU 1000 mg/9 wk	Oral TU 120-160 mg/d	9.97 (0.06, 2124.00)	9.93 (0.08, 1892.00)
IM TU 1000 mg/12 wk		0.86 (0.03, 44.86)	0.89 (0.04, 41.19)
IM TE 100 mg/wk		1.07 (0.01, 128.50)	1.18 (0.01, 158.90)
IM TE 125 mg/wk		12.28 (0.28, 1005.00)	13.78 (0.35, 940.60)
IM TE 150 mg/2 wk		1.34 (0.02, 149.00)	1.50 (0.02, 140.10)
IM TE 200 mg/2wk		4.70 (0.16, 248.70)	5.14 (0.19, 261.60)
IM TE 250 mg/3wk		6.63 (0.15, 519.00)	7.50 (0.19, 555.30)
IM TE 250 mg/4 wk		3.07 (0.05, 292.60)	3.26 (0.07, 258.70)
IM TE 300 mg/3wk		1.38 (0.03, 88.05)	1.38 (0.04, 77.22)
IM TE 50-400 mg/wk		1.31 (0.01, 140.60)	1.27 (0.01, 186.30)
IM TC 200 mg/2 wk		9.13 (0.21, 690.90)	9.97 (0.26, 696.80)
IM TU 1000 mg/12 wk	IM TU 1000 mg/9 wk	0.09 (0.00, 3.93)	0.09 (0.00, 3.90)
IM TE 100 mg/wk		0.11 (0.00, 15.20)	0.12 (0.00, 15.42)
IM TE 125 mg/wk		1.36 (0.01, 102.00)	1.45 (0.02, 91.32)
IM TE 150 mg/2 wk		0.15 (0.00, 14.29)	0.16 (0.00, 13.52)
IM TE 200 mg/2wk		0.52 (0.01, 25.88)	0.55 (0.01, 24.91)
IM TE 250 mg/3wk		0.75 (0.02, 19.79)	0.81 (0.02, 21.45)
IM TE 250 mg/4 wk		0.33 (0.00, 23.16)	0.34 (0.00, 24.45)
IM TE 300 mg/3wk		0.15 (0.00, 8.48)	0.15 (0.00, 7.46)
IM TE 50-400 mg/wk		0.13 (0.00, 17.85)	0.13 (0.00, 19.01)
IM TC 200 mg/2 wk		0.94 (0.01, 82.03)	1.05 (0.01, 65.82)

IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.25 (0.03, 33.94)	1.31 (0.03, 38.38)
IM TE 125 mg/wk		13.96 (1.53, 155.40)	14.83 (1.85, 160.90)
IM TE 150 mg/2 wk		1.65 (0.07, 26.87)	1.69 (0.08, 26.90)
IM TE 200 mg/2wk		5.35 (1.14, 29.79)	5.73 (1.27, 27.88)
IM TE 250 mg/3wk		7.46 (0.76, 95.56)	8.05 (0.92, 99.07)
IM TE 250 mg/4 wk		3.39 (0.27, 48.37)	3.56 (0.31, 46.26)
IM TE 300 mg/3wk		1.53 (0.20, 11.83)	1.56 (0.23, 9.85)
IM TE 50-400 mg/wk		1.39 (0.04, 43.58)	1.43 (0.03, 48.28)
IM TC 200 mg/2 wk		10.17 (1.09, 118.90)	10.69 (1.33, 115.60)
IM TE 125 mg/wk	IM TE 100 mg/wk	12.11 (0.25, 700.80)	11.59 (0.27, 834.30)
IM TE 150 mg/2 wk		1.31 (0.02, 102.10)	1.28 (0.02, 112.10)
IM TE 200 mg/2wk		4.42 (0.14, 212.20)	4.41 (0.14, 223.70)
IM TE 250 mg/3wk		6.48 (0.13, 403.60)	6.33 (0.14, 475.50)
IM TE 250 mg/4 wk		2.95 (0.05, 173.50)	2.79 (0.05, 218.80)
IM TE 300 mg/3wk		1.27 (0.03, 67.34)	1.19 (0.03, 67.28)
IM TE 50-400 mg/wk		1.12 (0.01, 151.40)	1.09 (0.01, 155.60)
IM TC 200 mg/2 wk		8.45 (0.20, 551.20)	8.46 (0.19, 575.20)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.11 (0.00, 3.07)	0.11 (0.00, 2.90)
IM TE 200 mg/2wk		0.38 (0.03, 4.28)	0.39 (0.03, 3.65)
IM TE 250 mg/3wk		0.53 (0.03, 12.61)	0.54 (0.03, 10.53)
IM TE 250 mg/4 wk		0.24 (0.01, 5.67)	0.24 (0.01, 5.01)
IM TE 300 mg/3wk		0.11 (0.01, 1.55)	0.10 (0.01, 1.25)
IM TE 50-400 mg/wk		0.10 (0.00, 4.20)	0.09 (0.00, 4.71)
IM TC 200 mg/2 wk		0.71 (0.04, 14.33)	0.72 (0.04, 13.09)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.30 (0.18, 86.63)	3.45 (0.19, 83.57)
IM TE 250 mg/3wk		4.82 (0.16, 184.20)	4.92 (0.18, 196.70)
IM TE 250 mg/4 wk		2.16 (0.06, 89.66)	2.16 (0.07, 89.94)
IM TE 300 mg/3wk		0.95 (0.04, 29.52)	0.92 (0.04, 25.90)
IM TE 50-400 mg/wk		0.87 (0.01, 61.14)	0.85 (0.01, 69.58)
IM TC 200 mg/2 wk		6.37 (0.22, 248.10)	6.46 (0.25, 248.50)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.37 (0.11, 20.90)	1.41 (0.13, 19.34)
IM TE 250 mg/4 wk		0.61 (0.04, 10.10)	0.62 (0.05, 8.87)
IM TE 300 mg/3wk		0.28 (0.03, 2.51)	0.27 (0.03, 1.99)
IM TE 50-400 mg/wk		0.26 (0.01, 8.14)	0.25 (0.01, 9.01)
IM TC 200 mg/2 wk		1.86 (0.16, 25.94)	1.88 (0.19, 22.98)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.44 (0.02, 10.79)	0.45 (0.02, 9.64)
IM TE 300 mg/3wk		0.20 (0.01, 3.27)	0.19 (0.01, 2.45)
IM TE 50-400 mg/wk		0.19 (0.00, 9.37)	0.17 (0.00, 9.07)
IM TC 200 mg/2 wk		1.36 (0.06, 30.52)	1.33 (0.07, 25.30)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.45 (0.02, 8.41)	0.43 (0.02, 6.70)
IM TE 50-400 mg/wk		0.40 (0.01, 24.86)	0.40 (0.01, 23.22)
IM TC 200 mg/2 wk		3.07 (0.12, 82.13)	3.02 (0.14, 67.09)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.90 (0.02, 37.63)	0.92 (0.02, 39.50)
IM TC 200 mg/2 wk		6.65 (0.47, 117.40)	6.99 (0.59, 107.90)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	7.58 (0.15, 503.50)	7.70 (0.15, 539.00)

Residual deviance	78.73 (81 points)	81.71 (81 points)
DIC	330.9	331.28

Withdrawals due to adverse events, continuity correction, treatments with zero events dropped: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
Patch 5 mg/d	Placebo	2.45 (0.79, 7.31)	2.62 (1.00, 7.06)
Gel 1% 5 mg/d		0.83 (0.31, 2.32)	0.80 (0.40, 1.58)
Gel 1% 50 mg/d		0.87 (0.46, 1.61)	0.90 (0.54, 1.48)
Gel 1% 75 mg/d		3.60 (0.45, 39.26)	3.52 (0.53, 35.24)
Gel 1%, 100 mg/wk		0.80 (0.33, 1.81)	0.83 (0.42, 1.59)
Gel 1.62% 40.5 mg/d		9.31 (1.26, 178.00)	10.35 (1.56, 192.70)
Gel 2% 60 mg/d		1.62 (0.53, 5.08)	1.63 (0.76, 3.63)
Oral TU 160 mg/d		1.02 (0.38, 2.89)	0.98 (0.45, 2.12)
IM TU 1000 mg/12 wk		0.43 (0.16, 1.17)	0.44 (0.17, 1.06)
IM TE 125 mg/wk		5.96 (0.79, 62.05)	6.42 (0.98, 63.12)
IM TE 150 mg/2 wk		0.73 (0.04, 11.04)	0.74 (0.04, 10.16)
IM TE 200 mg/2wk		2.38 (0.66, 9.73)	2.51 (0.76, 9.04)
IM TE 250 mg/3wk		4.07 (0.47, 60.27)	4.38 (0.57, 59.07)
IM TE 250 mg/4 wk		1.57 (0.15, 20.46)	1.57 (0.16, 16.85)
IM TE 300 mg/3wk		0.68 (0.10, 3.94)	0.68 (0.13, 3.23)
IM TC 200 mg/2 wk		4.28 (0.59, 49.63)	4.56 (0.73, 43.53)
Gel 1% 5 mg/d	Patch 5 mg/d	0.34 (0.08, 1.60)	0.30 (0.09, 0.98)
Gel 1% 50 mg/d		0.36 (0.11, 1.15)	0.34 (0.12, 0.92)
Gel 1% 75 mg/d		1.50 (0.14, 20.53)	1.36 (0.16, 15.94)
Gel 1%, 100 mg/wk		0.33 (0.10, 1.10)	0.32 (0.11, 0.87)
Gel 1.62% 40.5 mg/d		3.92 (0.38, 87.27)	4.03 (0.47, 85.56)
Gel 2% 60 mg/d		0.66 (0.15, 3.39)	0.62 (0.18, 2.20)
Oral TU 160 mg/d		0.42 (0.10, 1.99)	0.37 (0.11, 1.29)
IM TU 1000 mg/12 wk		0.18 (0.04, 0.80)	0.17 (0.04, 0.63)
IM TE 125 mg/wk		2.43 (0.25, 33.75)	2.47 (0.30, 29.26)
IM TE 150 mg/2 wk		0.30 (0.01, 5.43)	0.28 (0.01, 4.55)
IM TE 200 mg/2wk		0.97 (0.22, 4.85)	0.96 (0.23, 4.08)
IM TE 250 mg/3wk		1.70 (0.14, 30.02)	1.68 (0.17, 26.68)
IM TE 250 mg/4 wk		0.65 (0.05, 10.52)	0.60 (0.05, 7.78)
IM TE 300 mg/3wk		0.28 (0.03, 2.26)	0.26 (0.04, 1.65)
IM TC 200 mg/2 wk		1.79 (0.19, 25.38)	1.75 (0.22, 20.20)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.05 (0.31, 3.22)	1.13 (0.48, 2.64)
Gel 1% 75 mg/d		4.37 (0.43, 53.10)	4.46 (0.58, 48.20)
Gel 1%, 100 mg/wk		0.96 (0.24, 3.41)	1.03 (0.40, 2.67)
Gel 1.62% 40.5 mg/d		11.37 (1.16, 248.80)	13.17 (1.73, 260.60)
Gel 2% 60 mg/d		1.97 (0.43, 8.62)	2.04 (0.74, 5.87)
Oral TU 160 mg/d		1.23 (0.31, 5.09)	1.23 (0.44, 3.45)
IM TU 1000 mg/12 wk		0.52 (0.12, 2.08)	0.55 (0.17, 1.69)

IM TE 125 mg/wk		7.22 (0.75, 88.54)	8.15 (1.11, 84.13)
IM TE 150 mg/2 wk		0.87 (0.04, 15.56)	0.93 (0.05, 13.89)
IM TE 200 mg/2wk		2.88 (0.56, 15.29)	3.14 (0.80, 13.32)
IM TE 250 mg/3wk		4.95 (0.44, 89.63)	5.56 (0.64, 80.40)
IM TE 250 mg/4 wk		1.89 (0.15, 28.44)	1.96 (0.19, 23.31)
IM TE 300 mg/3wk		0.81 (0.10, 5.99)	0.85 (0.14, 4.74)
IM TC 200 mg/2 wk		5.17 (0.57, 69.47)	5.75 (0.81, 60.51)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	4.14 (0.47, 48.50)	3.96 (0.55, 40.98)
Gel 1%, 100 mg/wk		0.91 (0.34, 2.44)	0.92 (0.41, 2.01)
Gel 1.62% 40.5 mg/d		10.70 (1.35, 219.60)	11.67 (1.61, 222.80)
Gel 2% 60 mg/d		1.87 (0.52, 7.02)	1.82 (0.73, 4.69)
Oral TU 160 mg/d		1.17 (0.37, 4.11)	1.09 (0.43, 2.75)
IM TU 1000 mg/12 wk		0.50 (0.15, 1.62)	0.49 (0.16, 1.36)
IM TE 125 mg/wk		6.86 (0.83, 77.16)	7.16 (1.03, 72.35)
IM TE 150 mg/2 wk		0.84 (0.04, 13.73)	0.83 (0.04, 11.87)
IM TE 200 mg/2wk		2.74 (0.68, 12.47)	2.80 (0.77, 10.91)
IM TE 250 mg/3wk		4.71 (0.50, 74.22)	4.92 (0.59, 68.17)
IM TE 250 mg/4 wk		1.78 (0.17, 25.43)	1.74 (0.17, 20.13)
IM TE 300 mg/3wk		0.77 (0.11, 5.07)	0.76 (0.13, 3.89)
IM TC 200 mg/2 wk		4.96 (0.63, 60.52)	5.09 (0.75, 51.39)
Gel 1%, 100 mg/wk	Gel 1% 75 mg/d	0.22 (0.02, 2.08)	0.23 (0.02, 1.74)
Gel 1.62% 40.5 mg/d		2.68 (0.12, 89.97)	3.06 (0.14, 90.93)
Gel 2% 60 mg/d		0.45 (0.03, 5.09)	0.46 (0.04, 3.65)
Oral TU 160 mg/d		0.28 (0.02, 2.91)	0.28 (0.02, 2.13)
IM TU 1000 mg/12 wk		0.12 (0.01, 1.21)	0.12 (0.01, 1.01)
IM TE 125 mg/wk		1.65 (0.08, 39.04)	1.83 (0.10, 34.36)
IM TE 150 mg/2 wk		0.20 (0.00, 6.22)	0.20 (0.01, 5.41)
IM TE 200 mg/2wk		0.66 (0.04, 8.08)	0.70 (0.06, 7.14)
IM TE 250 mg/3wk		1.15 (0.04, 33.64)	1.25 (0.06, 30.02)
IM TE 250 mg/4 wk		0.43 (0.02, 11.15)	0.43 (0.02, 9.51)
IM TE 300 mg/3wk		0.18 (0.01, 2.84)	0.19 (0.01, 2.29)
IM TC 200 mg/2 wk		1.21 (0.05, 28.54)	1.30 (0.07, 24.36)
Gel 1.62% 40.5 mg/d	Gel 1%, 100 mg/wk	11.93 (1.31, 242.20)	12.74 (1.70, 246.90)
Gel 2% 60 mg/d		2.05 (0.52, 8.87)	1.98 (0.72, 5.63)
Oral TU 160 mg/d		1.28 (0.36, 5.22)	1.18 (0.43, 3.30)
IM TU 1000 mg/12 wk		0.54 (0.15, 2.10)	0.53 (0.17, 1.62)
IM TE 125 mg/wk		7.48 (0.85, 92.34)	7.82 (1.08, 83.28)
IM TE 150 mg/2 wk		0.93 (0.04, 15.61)	0.89 (0.05, 13.42)
IM TE 200 mg/2wk		3.01 (0.67, 14.99)	3.04 (0.79, 12.45)
IM TE 250 mg/3wk		5.21 (0.49, 87.36)	5.38 (0.61, 76.27)
IM TE 250 mg/4 wk		2.00 (0.17, 28.89)	1.91 (0.18, 22.65)
IM TE 300 mg/3wk		0.85 (0.11, 6.13)	0.83 (0.14, 4.48)
IM TC 200 mg/2 wk		5.47 (0.64, 71.24)	5.55 (0.77, 58.52)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.17 (0.01, 1.80)	0.15 (0.01, 1.25)
Oral TU 160 mg/d		0.11 (0.01, 1.08)	0.09 (0.00, 0.74)

IM TU 1000 mg/12 wk		0.04 (0.00, 0.46)	0.04 (0.00, 0.34)
IM TE 125 mg/wk		0.61 (0.02, 14.21)	0.60 (0.02, 11.69)
IM TE 150 mg/2 wk		0.07 (0.00, 2.40)	0.07 (0.00, 1.89)
IM TE 200 mg/2wk		0.25 (0.01, 2.95)	0.24 (0.01, 2.37)
IM TE 250 mg/3wk		0.44 (0.01, 11.97)	0.41 (0.01, 10.31)
IM TE 250 mg/4 wk		0.16 (0.00, 4.16)	0.14 (0.00, 3.19)
IM TE 300 mg/3wk		0.07 (0.00, 1.04)	0.06 (0.00, 0.79)
IM TC 200 mg/2 wk		0.44 (0.01, 11.78)	0.42 (0.01, 8.57)
Oral TU 160 mg/d	Gel 2% 60 mg/d	0.63 (0.14, 2.94)	0.60 (0.20, 1.78)
IM TU 1000 mg/12 wk		0.27 (0.06, 1.16)	0.27 (0.08, 0.88)
IM TE 125 mg/wk		3.65 (0.37, 50.10)	3.94 (0.52, 42.71)
IM TE 150 mg/2 wk		0.45 (0.02, 8.54)	0.45 (0.02, 6.96)
IM TE 200 mg/2wk		1.47 (0.25, 8.77)	1.54 (0.37, 6.79)
IM TE 250 mg/3wk		2.53 (0.22, 45.79)	2.71 (0.29, 40.07)
IM TE 250 mg/4 wk		0.96 (0.07, 15.99)	0.96 (0.09, 11.81)
IM TE 300 mg/3wk		0.41 (0.05, 3.38)	0.42 (0.06, 2.39)
IM TC 200 mg/2 wk		2.66 (0.26, 38.71)	2.81 (0.38, 30.34)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.42 (0.10, 1.66)	0.45 (0.13, 1.46)
IM TE 125 mg/wk		5.87 (0.62, 72.39)	6.58 (0.88, 71.91)
IM TE 150 mg/2 wk		0.71 (0.03, 12.90)	0.76 (0.04, 11.85)
IM TE 200 mg/2wk		2.37 (0.44, 12.74)	2.56 (0.62, 11.32)
IM TE 250 mg/3wk		4.03 (0.36, 66.58)	4.51 (0.50, 67.62)
IM TE 250 mg/4 wk		1.54 (0.12, 23.72)	1.61 (0.14, 19.81)
IM TE 300 mg/3wk		0.67 (0.07, 4.97)	0.70 (0.11, 3.95)
IM TC 200 mg/2 wk		4.24 (0.45, 58.34)	4.70 (0.63, 50.66)
IM TE 125 mg/wk	IM TU 1000 mg/12 wk	13.85 (1.49, 175.80)	14.85 (1.85, 172.60)
IM TE 150 mg/2 wk		1.70 (0.08, 30.34)	1.70 (0.08, 27.58)
IM TE 200 mg/2wk		5.53 (1.13, 30.54)	5.76 (1.28, 27.78)
IM TE 250 mg/3wk		9.41 (0.88, 175.80)	10.17 (1.06, 156.50)
IM TE 250 mg/4 wk		3.67 (0.29, 54.69)	3.59 (0.32, 46.88)
IM TE 300 mg/3wk		1.58 (0.19, 11.91)	1.56 (0.23, 9.59)
IM TC 200 mg/2 wk		9.98 (1.08, 139.70)	10.62 (1.33, 118.60)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.12 (0.00, 3.33)	0.11 (0.00, 2.86)
IM TE 200 mg/2wk		0.40 (0.03, 4.48)	0.39 (0.03, 3.77)
IM TE 250 mg/3wk		0.68 (0.03, 22.04)	0.68 (0.03, 16.64)
IM TE 250 mg/4 wk		0.26 (0.01, 6.42)	0.24 (0.01, 5.01)
IM TE 300 mg/3wk		0.11 (0.01, 1.68)	0.10 (0.01, 1.20)
IM TC 200 mg/2 wk		0.73 (0.03, 17.95)	0.71 (0.04, 13.26)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.25 (0.17, 85.05)	3.45 (0.19, 80.34)
IM TE 250 mg/3wk		5.83 (0.18, 293.90)	6.26 (0.21, 278.90)
IM TE 250 mg/4 wk		2.19 (0.06, 98.17)	2.17 (0.07, 89.08)
IM TE 300 mg/3wk		0.92 (0.04, 29.16)	0.92 (0.04, 24.77)
IM TC 200 mg/2 wk		6.07 (0.21, 269.50)	6.38 (0.25, 234.20)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	1.73 (0.13, 33.29)	1.77 (0.16, 30.63)
IM TE 250 mg/4 wk		0.66 (0.05, 10.99)	0.62 (0.05, 8.85)

IM TE 300 mg/3wk		0.28 (0.03, 2.53)	0.27 (0.03, 1.94)
IM TC 200 mg/2 wk		1.83 (0.16, 27.09)	1.83 (0.19, 22.86)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.37 (0.01, 10.73)	0.35 (0.01, 8.32)
IM TE 300 mg/3wk		0.16 (0.01, 2.64)	0.15 (0.01, 2.07)
IM TC 200 mg/2 wk		1.06 (0.04, 28.28)	1.03 (0.04, 22.03)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.43 (0.02, 7.93)	0.43 (0.02, 6.89)
IM TC 200 mg/2 wk		2.80 (0.11, 71.27)	2.96 (0.14, 69.92)
IM TC 200 mg/2 wk	IM TE 300 mg/3wk	6.53 (0.44, 127.90)	6.84 (0.58, 111.00)
Residual deviance		71.63 (71 points)	74.37 (71 points)
DIC		302.57	302.53

Subgroups: by route of administration

Cardiovascular death, by route, base case (no continuity correction): Odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	1.30 (0.43, 3.99)	1.36 (0.39, 4.81)
IM		0.61 (0.15, 2.08)	0.05 (0.37, 1.74)
Oral		0.50 (0.03, 4.81)	0.00 (0.12, 4.10)
IM	Topical	0.46 (0.08, 2.55)	0.03 (0.27, 1.99)
Oral		0.39 (0.02, 4.92)	0.00 (0.08, 3.46)
Oral	IM	0.82 (0.04, 11.82)	0.00 (0.31, 17.83)
Residual Deviance		25.42 (28 points)	26.13 (28 points)
DIC		58.434	58.6

Cardiovascular death, by route, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	1.30 (0.43, 3.99)	1.32 (0.48, 3.70)
IM		0.61 (0.15, 2.08)	0.62 (0.17, 2.02)
Oral		0.50 (0.03, 4.81)	0.52 (0.03, 5.02)
IM	Topical	0.46 (0.08, 2.55)	0.47 (0.09, 2.22)
Oral		0.39 (0.02, 4.92)	0.39 (0.02, 4.77)
Oral	IM	0.82 (0.04, 11.82)	0.83 (0.04, 11.33)
Residual Deviance		20.25 (25 points)	20.25 (25 points)
DIC		83.75	83.108

Myocardial infarction, by route, no continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	0.43 (0.06, 2.13)	0.46 (0.09, 1.98)

IM		0.19 (0.02, 1.01)	0.22 (0.03, 1.01)
Oral		0.05 (0.00, 1.31)	0.05 (0.00, 1.09)
IM	Topical	0.45 (0.03, 5.41)	0.47 (0.04, 4.40)
Oral		0.12 (0.00, 5.86)	0.11 (0.00, 3.72)
Oral	IM	0.27 (0.00, 14.14)	0.25 (0.00, 8.15)
Residual Deviance		21.04 (21 points)	22.8 (21 points)
DIC		59.93	54.93

Myocardial infarction, by route, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	0.65 (0.18, 2.25)	0.67 (0.20, 2.12)
IM		0.32 (0.07, 1.28)	0.33 (0.08, 1.20)
Oral		0.22 (0.01, 2.89)	0.23 (0.01, 2.80)
IM	Topical	0.49 (0.08, 3.24)	0.49 (0.08, 2.87)
Oral		0.33 (0.01, 6.11)	0.34 (0.01, 5.60)
Oral	IM	0.66 (0.02, 13.39)	0.69 (0.02, 12.26)
Residual Deviance		16.91 (21 points)	17.29 (21 points)
DIC		67.49	67.24

Prostate cancer, by route, base case (no continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	0.59 (0.14, 2.17)	0.58 (0.14, 2.09)
IM		0.57 (0.16, 1.89)	0.58 (0.17, 1.76)
Oral		0.06 (0.00, 1.58)	0.06 (0.00, 1.29)
IM	Topical	0.97 (0.19, 4.80)	1.00 (0.23, 4.60)
Oral		0.11 (0.00, 3.93)	0.10 (0.00, 3.07)
Oral	IM	0.11 (0.00, 3.70)	0.10 (0.00, 2.82)
Residual Deviance		17.83 (20 points)	17.93 (20 points)
DIC		59.07	57.53

Prostate cancer, by route, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	0.70 (0.20, 2.32)	0.69 (0.21, 2.12)
IM		0.65 (0.21, 2.05)	0.66 (0.22, 1.84)
Oral		0.17 (0.01, 1.86)	0.18 (0.01, 1.84)
IM	Topical	0.95 (0.22, 4.02)	0.95 (0.24, 3.76)
Oral		0.23 (0.01, 3.72)	0.25 (0.01, 3.46)

Oral	IM	0.25 (0.01, 3.72)	0.26 (0.01, 3.58)
Residual Deviance		15.32 (20 points)	15.31 (20 points)
DIC		68.44	67.928

Serious adverse events, by route, no continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	1.15 (0.61, 2.14)	1.21 (0.73, 2.03)
IM		0.60 (0.19, 1.64)	0.63 (0.21, 1.65)
Oral		0.43 (0.11, 1.58)	0.44 (0.14, 1.26)
IM	Topical	0.52 (0.15, 1.58)	0.52 (0.16, 1.44)
Oral		0.38 (0.09, 1.64)	0.36 (0.10, 1.17)
Oral	IM	0.73 (0.13, 4.02)	0.70 (0.16, 3.16)
Residual Deviance		22.27 (25 points)	23.25 (25 points)
DIC		100.42	100.12

Serious adverse events, by route (continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects model	Fixed-effects model
Topical	Placebo	1.16 (0.62, 2.12)	1.21 (0.73, 2.03)
IM		0.63 (0.20, 1.73)	0.64 (0.23, 1.67)
Oral		0.45 (0.12, 1.54)	0.45 (0.14, 1.25)
IM	Topical	0.54 (0.16, 1.63)	0.53 (0.17, 1.44)
Oral		0.38 (0.09, 1.56)	0.37 (0.10, 1.16)
Oral	IM	0.72 (0.13, 3.78)	0.70 (0.16, 2.93)
Residual Deviance		21.06 (25 points)	21.87 (25 points)
DIC		106.04	105.46

Withdrawals due to adverse events, by route, base case (no continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
Topical	Placebo	1.13 (0.72, 1.78)	1.11 (0.82, 1.52)
IM		1.14 (0.60, 2.10)	1.15 (0.67, 1.98)
Oral		0.86 (0.28, 2.59)	0.88 (0.40, 1.93)
IM	topical	1.01 (0.47, 2.13)	1.03 (0.56, 1.93)
Oral		0.77 (0.23, 2.47)	0.79 (0.34, 1.85)
Oral	IM	0.76 (0.22, 2.67)	0.76 (0.29, 2.00)
Residual deviance		86.76 (76 points)	96.15 (76 points)
DIC		274.84	277.98

Withdrawals due to adverse events, by route, continuity correction: odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
topical	Placebo	1.13 (0.77, 1.71)	1.11 (0.82, 1.51)
IM		1.18 (0.67, 2.07)	1.19 (0.71, 1.99)
Oral		0.96 (0.39, 2.32)	0.93 (0.44, 1.93)
IM	topical	1.04 (0.52, 2.03)	1.07 (0.59, 1.93)
Oral		0.84 (0.32, 2.22)	0.84 (0.38, 1.86)
Oral	IM	0.82 (0.28, 2.35)	0.78 (0.32, 1.90)
Residual deviance		77.25 (76 points)	83.29 (76 points)
DIC		305.121	306.29

Subgroups: by treatment duration

Cardiovascular death, treatment duration 6 months or longer, continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed effects
Gel 1% 50 mg/d	Placebo	1.45(0.23,10.50)	1.45(0.25,9.35)
1% gel, 100 mg/d		1.49(0.11,23.29)	1.48(0.12,22.01)
1.62% gel, 40.5 mg/d		0.35(0.01,10.86)	0.35(0.01,9.59)
2% gel, 60 mg/d		0.25(0.01,3.50)	0.26(0.01,3.43)
Oral TU 120 or 160 mg/d		0.50(0.01,10.76)	0.50(0.01,10.48)
IM TU 1000 mg/12 wk		0.69(0.14,3.19)	0.69(0.15,2.93)
IM TE 200 mg/2wk		0.58(0.01,15.04)	0.55(0.01,13.19)
IM TE 250 mg/3 wk		0.43(0.01,12.92)	0.42(0.01,12.54)
1% gel, 100 mg/d	Gel 1% 50 mg/d	1.01(0.04,29.96)	1.01(0.04,24.73)
1.62% gel, 40.5 mg/d		0.24(0.01,11.70)	0.24(0.01,9.80)
2% gel, 60 mg/d		0.16(0.00,4.73)	0.17(0.00,4.11)
Oral TU 120 or 160 mg/d		0.34(0.01,12.25)	0.33(0.01,11.67)
IM TU 1000 mg/12 wk		0.47(0.04,5.20)	0.47(0.04,4.66)
IM TE 200 mg/2wk		0.39(0.01,16.71)	0.37(0.01,14.49)
IM TE 250 mg/3 wk		0.29(0.00,14.26)	0.28(0.00,13.50)
1.62% gel, 40.5 mg/d	1% gel, 100 mg/d	0.25(0.00,16.16)	0.24(0.00,15.01)
2% gel, 60 mg/d		0.16(0.00,8.09)	0.17(0.00,6.98)
Oral TU 120 or 160 mg/d		0.33(0.00,18.92)	0.32(0.00,17.96)
IM TU 1000 mg/12 wk		0.47(0.02,9.58)	0.46(0.02,8.48)
IM TE 200 mg/2wk		0.38(0.00,22.36)	0.36(0.00,22.08)
IM TE 250 mg/3 wk		0.28(0.00,21.56)	0.28(0.00,19.37)
2% gel, 60 mg/d	1.62% gel, 40.5 mg/d	0.67(0.01,41.61)	0.70(0.01,42.62)
Oral TU 120 or 160 mg/d		1.40(0.01,146.80)	1.35(0.01,114.10)
IM TU 1000 mg/12 wk		1.98(0.04,71.50)	1.95(0.05,63.59)
IM TE 200 mg/2wk		1.54(0.01,178.30)	1.51(0.01,137.10)

IM TE 250 mg/3 wk		1.22(0.01,128.50)	1.16(0.01,126.00)
Oral TU 120 or 160 mg/d	2% gel, 60 mg/d	2.22(0.02,178.90)	1.94(0.02,199.80)
IM TU 1000 mg/12 wk		2.87(0.12,126.00)	2.69(0.13,121.40)
IM TE 200 mg/2wk		2.36(0.02,298.70)	2.18(0.02,230.40)
IM TE 250 mg/3 wk		1.81(0.02,222.90)	1.70(0.02,220.50)
IM TU 1000 mg/12 wk	Oral TU 120 or 160 mg/d	1.34(0.04,81.75)	1.40(0.05,78.25)
IM TE 200 mg/2wk		1.18(0.01,127.10)	1.12(0.01,148.50)
IM TE 250 mg/3 wk		0.83(0.01,129.40)	0.88(0.01,132.00)
IM TE 200 mg/2wk	IM TU 1000 mg/12 wk	0.82(0.01,30.93)	0.79(0.01,27.97)
IM TE 250 mg/3 wk		0.63(0.02,15.34)	0.63(0.01,16.04)
IM TE 250 mg/3 wk	IM TE 200 mg/2wk	0.76(0.00,109.00)	0.78(0.01,120.70)
Residual deviance		16.35 (22 points)	16.38 (22 points)
DIC		69.91	69.97

Prostate cancer, treatment duration 6 months or longer, continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
Gel 5 mg/d	Placebo	0.61(0.03,8.64)	0.63(0.03,7.68)
Gel 1% 50 mg/d		0.63(0.07,4.07)	0.65(0.09,3.86)
Gel 1% 100 mg/d		1.46(0.10,24.72)	1.46(0.11,20.09)
Oral TU 160 mg/d		0.17(0.00,1.97)	0.17(0.01,1.77)
IM TU 1000 mg/12 wk		0.27(0.01,4.19)	0.26(0.01,3.41)
IM TE 150 mg/2wk		0.41(0.05,2.85)	0.42(0.06,2.36)
IM TE 200 mg/2wk		1.60(0.14,20.43)	1.55(0.16,16.90)
IM TE 250 mg/4wk		0.59(0.01,14.32)	0.55(0.01,12.69)
Gel 1% 50 mg/d	Gel 5 mg/d	1.02(0.04,33.49)	1.03(0.04,30.32)
Gel 1% 100 mg/d		2.42(0.06,140.90)	2.38(0.07,110.80)
Oral TU 160 mg/d		0.27(0.00,13.67)	0.26(0.00,10.77)
IM TU 1000 mg/12 wk		0.42(0.00,26.06)	0.40(0.01,19.34)
IM TE 150 mg/2wk		0.66(0.02,21.03)	0.67(0.03,19.16)
IM TE 200 mg/2wk		2.72(0.07,121.80)	2.54(0.08,100.40)
IM TE 250 mg/4wk		0.93(0.01,78.30)	0.86(0.01,61.33)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	2.36(0.10,71.99)	2.30(0.10,60.60)
Oral TU 160 mg/d		0.25(0.01,7.14)	0.26(0.01,5.76)
IM TU 1000 mg/12 wk		0.42(0.01,13.09)	0.39(0.01,10.37)
IM TE 150 mg/2wk		0.64(0.04,11.27)	0.65(0.05,8.88)
IM TE 200 mg/2wk		2.58(0.12,67.79)	2.44(0.14,52.58)
IM TE 250 mg/4wk		0.93(0.01,40.53)	0.84(0.01,34.65)
Oral TU 160 mg/d	Gel 1% 100 mg/d	0.11(0.00,4.64)	0.11(0.00,3.74)
IM TU 1000 mg/12 wk		0.17(0.00,8.49)	0.17(0.00,6.99)
IM TE 150 mg/2wk		0.27(0.01,7.46)	0.28(0.01,6.26)
IM TE 200 mg/2wk		1.07(0.03,44.37)	1.07(0.03,33.77)

IM TE 250 mg/4wk		0.38(0.00,27.49)	0.36(0.00,21.20)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	1.74(0.02,125.60)	1.54(0.02,101.50)
IM TE 150 mg/2wk		2.44(0.09,146.70)	2.47(0.12,109.90)
IM TE 200 mg/2wk		10.06(0.25,855.80)	9.69(0.33,538.00)
IM TE 250 mg/4wk		3.60(0.03,379.10)	3.38(0.04,311.20)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	1.51(0.05,86.89)	1.65(0.06,81.96)
IM TE 200 mg/2wk		6.21(0.15,510.50)	6.34(0.19,425.40)
IM TE 250 mg/4wk		2.16(0.02,282.30)	2.19(0.02,247.80)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	4.01(0.16,117.00)	3.77(0.21,77.92)
IM TE 250 mg/4wk		1.44(0.02,70.26)	1.30(0.02,53.01)
IM TE 250 mg/4wk	IM TE 200 mg/2wk	0.35(0.00,21.02)	0.34(0.00,16.22)
Residual deviance		221.6 (18 points)	15.19 (18 points)
DIC		66.16	65.96

Serious adverse events, treatment duration 6 months or longer, continuity correction): odds ratio (95% CrI)
— random-effects and fixed-effects models

Treatment	Reference	Random-effects	Fixed-effects
Patch 4.8 mg/d	Placebo	0.29(0.01,7.30)	0.26(0.01,6.06)
Gel 1% 50 mg/d		1.31(0.49,3.69)	1.34(0.57,3.17)
Gel 1% 100 mg/d		2.07(0.64,6.70)	2.06(0.87,5.19)
Gel 1.62% 40.5 mg/d		0.74(0.12,7.00)	0.73(0.13,6.81)
Oral TU 160 mg/d		0.44(0.11,1.52)	0.44(0.14,1.25)
IM TU 1000 mg/12 wk		0.39(0.10,1.37)	0.37(0.10,1.16)
IM TE 250 mg/3 wk		0.42(0.02,8.65)	0.38(0.02,7.07)
Gel 1% 50 mg/d	Patch 4.8 mg/d	4.48(0.16,127.10)	5.19(0.20,135.00)
Gel 1% 100 mg/d		7.11(0.23,206.90)	7.95(0.31,215.30)
Gel 1.62% 40.5 mg/d		2.74(0.06,118.10)	2.97(0.08,128.60)
Oral TU 160 mg/d		1.48(0.05,44.39)	1.68(0.06,46.49)
IM TU 1000 mg/12 wk		1.28(0.06,31.88)	1.40(0.06,32.94)
IM TE 250 mg/3 wk		1.48(0.26,6.80)	1.53(0.31,5.53)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.58(0.32,7.26)	1.55(0.46,5.38)
Gel 1.62% 40.5 mg/d		0.57(0.07,6.39)	0.55(0.08,5.94)
Oral TU 160 mg/d		0.33(0.06,1.63)	0.33(0.08,1.28)
IM TU 1000 mg/12 wk		0.29(0.05,1.43)	0.27(0.06,1.16)
IM TE 250 mg/3 wk		0.32(0.01,7.49)	0.29(0.01,6.08)
Gel 1.62% 40.5 mg/d	Gel 1% 100 mg/d	0.36(0.04,4.46)	0.36(0.05,3.86)
Oral TU 160 mg/d		0.21(0.04,1.19)	0.21(0.05,0.83)
IM TU 1000 mg/12 wk		0.19(0.03,1.04)	0.18(0.04,0.75)
IM TE 250 mg/3 wk		0.20(0.01,5.17)	0.19(0.01,3.86)
Oral TU 160 mg/d	Gel 1.62% 40.5 mg/d	0.58(0.04,5.55)	0.59(0.05,4.45)
IM TU 1000 mg/12 wk		0.50(0.04,4.67)	0.49(0.04,4.03)
IM TE 250 mg/3 wk		0.54(0.01,20.13)	0.50(0.01,15.46)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.87(0.14,5.27)	0.83(0.16,4.14)

IM TE 250 mg/3 wk		1.00(0.04,23.45)	0.87(0.04,20.02)
IM TE 250 mg/3 wk	IM TU 1000 mg/12 wk	1.12(0.06,20.83)	1.06(0.05,19.43)
Residual deviance		16.41 (21 points)	16.19 (21 points)
DIC		91.29	91.74

Withdrawals due to adverse events, treatment duration less than 6 months, continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	OR (95% CrI)	Fixed-effects
Patch 5 mg/d	placebo	3.42(0.54,18.50)	4.35(1.31,16.05)
Gel 1% 50 mg/d		0.91(0.25,3.01)	1.03(0.43,2.49)
Gel 1% 75 mg/d		3.40(0.27,51.69)	3.66(0.53,35.94)
Gel 1% 100 mg/d		0.78(0.11,4.02)	0.93(0.26,3.11)
Oral TU 120 mg/d		0.53(0.01,17.84)	0.56(0.01,12.90)
Oral TU 160 mg/d		3.00(0.19,59.70)	2.98(0.32,42.00)
IM TU 1000 mg/12 wk		0.56(0.01,17.21)	0.53(0.01,11.86)
IM TE 100 mg/wk		0.56(0.01,18.09)	0.58(0.01,14.79)
IM TE 200 mg/2wk		2.23(0.15,27.83)	2.80(0.27,26.21)
Gel 1% 50 mg/d	Patch 5 mg/d	0.27(0.05,1.68)	0.24(0.06,0.76)
Gel 1% 75 mg/d		1.00(0.05,26.46)	0.83(0.08,11.04)
Gel 1% 100 mg/d		0.23(0.03,1.71)	0.21(0.05,0.73)
Oral TU 120 mg/d		0.15(0.00,8.66)	0.13(0.00,3.74)
Oral TU 160 mg/d		0.89(0.04,29.95)	0.69(0.05,12.75)
IM TU 1000 mg/12 wk		0.16(0.00,7.86)	0.12(0.00,3.48)
IM TE 100 mg/wk		0.16(0.00,8.37)	0.13(0.00,4.10)
IM TE 200 mg/2wk		0.66(0.05,8.46)	0.65(0.06,5.66)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	3.76(0.23,79.09)	3.57(0.43,40.84)
Gel 1% 100 mg/d		0.85(0.11,5.57)	0.90(0.23,3.37)
Oral TU 120 mg/d		0.58(0.01,25.06)	0.54(0.01,13.97)
Oral TU 160 mg/d		3.33(0.17,89.28)	2.92(0.26,47.85)
IM TU 1000 mg/12 wk		0.60(0.01,25.26)	0.51(0.01,12.88)
IM TE 100 mg/wk		0.62(0.01,24.98)	0.56(0.01,15.77)
IM TE 200 mg/2wk		2.43(0.15,37.00)	2.73(0.24,28.08)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	0.22(0.01,4.57)	0.25(0.02,2.53)
Oral TU 120 mg/d		0.15(0.00,13.54)	0.14(0.00,6.07)
Oral TU 160 mg/d		0.89(0.02,47.57)	0.82(0.03,20.35)
IM TU 1000 mg/12 wk		0.15(0.00,12.34)	0.14(0.00,5.59)
IM TE 100 mg/wk		0.16(0.00,12.51)	0.15(0.00,6.72)
IM TE 200 mg/2wk		0.64(0.01,21.48)	0.75(0.03,14.99)
Oral TU 120 mg/d	Gel 1% 100 mg/d	0.70(0.01,40.06)	0.60(0.01,18.03)
Oral TU 160 mg/d		3.96(0.16,148.30)	3.30(0.25,58.84)
IM TU 1000 mg/12 wk		0.71(0.01,38.23)	0.57(0.01,16.27)
IM TE 100 mg/wk		0.75(0.01,36.96)	0.62(0.01,20.00)
IM TE 200 mg/2wk		2.93(0.15,58.47)	3.05(0.25,34.03)
Oral TU 160 mg/d	Oral TU 120 mg/d	5.89(0.07,791.50)	5.74(0.12,513.10)

IM TU 1000 mg/12 wk		0.99(0.00,212.40)	0.96(0.01,130.80)
IM TE 100 mg/wk		1.07(0.01,195.70)	1.03(0.01,146.10)
IM TE 200 mg/2wk		4.31(0.05,414.70)	5.15(0.10,414.00)
IM TU 1000 mg/12 wk	Oral TU 160 mg/d	0.18(0.00,13.64)	0.17(0.00,8.61)
IM TE 100 mg/wk		0.18(0.00,15.17)	0.18(0.00,9.96)
IM TE 200 mg/2wk		0.73(0.01,30.61)	0.92(0.03,23.04)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.08(0.01,176.80)	1.10(0.01,147.50)
IM TE 200 mg/2wk		4.11(0.05,468.60)	5.42(0.11,404.30)
IM TE 200 mg/2wk	IM TE 100 mg/wk	4.03(0.05,414.60)	4.92(0.09,366.30)
Residual deviance		30.29 (29 points)	36.77(29 points)
DIC		112.23	116.12

Withdrawals due to adverse events, treatment duration 6 months or longer, continuity correction): odds ratio (95% CrI) — random-effects and fixed-effects models

Treatment	Reference	OR (95% CrI)	RR (95% CrI)
Patch 5 mg/d	Placebo	0.25(0.01,3.68)	0.27(0.01,3.89)
Gel 1% 5 mg/d		0.76(0.28,1.99)	0.75(0.37,1.52)
Gel 1% 50 mg/d		0.89(0.41,1.90)	0.90(0.48,1.65)
Gel 1% 100 mg/d		0.89(0.31,2.52)	0.88(0.39,1.96)
Gel 1.62% 40.5 mg/d		8.59(1.29,134.20)	8.41(1.47,156.50)
Gel 2% 60 mg/d		1.62(0.58,4.61)	1.63(0.76,3.61)
Oral TU 160 mg/d		0.84(0.29,2.35)	0.84(0.37,1.94)
Oral TU 120-160 mg/d		0.53(0.01,12.28)	0.50(0.01,10.90)
IM TU 1000 mg/12 wk		0.49(0.18,1.30)	0.50(0.19,1.23)
IM TE 125 mg/wk		6.38(0.86,57.20)	6.35(1.01,62.15)
IM TE 150 mg/2 wk		0.79(0.04,10.60)	0.74(0.04,10.22)
IM TE 200 mg/2wk		2.61(0.58,13.71)	2.61(0.62,12.58)
IM TE 250 mg/3wk		1.95(0.30,13.79)	1.98(0.35,14.00)
IM TE 250 mg/4 wk		1.50(0.17,17.85)	1.56(0.16,16.90)
IM TE 300 mg/3wk		0.66(0.11,3.75)	0.68(0.12,3.33)
IM TE 50-400 mg/wk		0.57(0.01,15.72)	0.62(0.01,19.93)
IM TC 200 mg/2 wk		4.60(0.63,41.23)	4.57(0.72,47.23)
Gel 1% 5 mg/d	Patch 5 mg/d	3.05(0.17,111.10)	2.81(0.18,99.63)
Gel 1% 50 mg/d		3.56(0.22,120.50)	3.32(0.22,120.10)
Gel 1% 100 mg/d		3.58(0.19,136.10)	3.28(0.20,120.20)
Gel 1.62% 40.5 mg/d		37.35(1.22,2493.00)	34.98(1.22,2863.00)
Gel 2% 60 mg/d		6.51(0.36,247.20)	6.14(0.37,222.40)
Oral TU 160 mg/d		3.34(0.18,118.60)	3.14(0.20,118.20)
Oral TU 120-160 mg/d		2.07(0.03,212.10)	1.87(0.02,192.50)
IM TU 1000 mg/12 wk		1.99(0.11,70.73)	1.86(0.11,69.09)
IM TE 125 mg/wk		25.95(0.86,1460.00)	25.49(0.88,1472.00)
IM TE 150 mg/2 wk		3.12(0.06,245.60)	2.82(0.05,204.20)
IM TE 200 mg/2wk		10.54(0.45,457.30)	10.01(0.47,454.30)
IM TE 250 mg/3wk		7.94(0.30,377.00)	7.79(0.30,387.00)

IM TE 250 mg/4 wk		6.29(0.17,438.20)	6.11(0.17,375.10)
IM TE 300 mg/3wk		2.68(0.11,121.80)	2.56(0.10,117.00)
IM TE 50-400 mg/wk		2.38(0.02,250.90)	2.47(0.03,303.00)
IM TC 200 mg/2 wk		19.26(0.62,985.50)	18.26(0.66,1118.00)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	1.18(0.34,4.06)	1.18(0.47,3.04)
Gel 1% 100 mg/d		1.17(0.28,4.94)	1.16(0.39,3.41)
Gel 1.62% 40.5 mg/d		11.49(1.33,200.30)	11.23(1.67,220.30)
Gel 2% 60 mg/d		2.15(0.52,8.98)	2.16(0.77,6.27)
Oral TU 160 mg/d		1.10(0.26,4.53)	1.12(0.38,3.34)
Oral TU 120-160 mg/d		0.71(0.01,19.63)	0.65(0.01,15.79)
IM TU 1000 mg/12 wk		0.65(0.16,2.60)	0.66(0.20,2.09)
IM TE 125 mg/wk		8.48(0.89,93.51)	8.47(1.18,90.35)
IM TE 150 mg/2 wk		1.05(0.05,16.85)	0.98(0.05,14.62)
IM TE 200 mg/2wk		3.45(0.57,23.52)	3.45(0.71,19.59)
IM TE 250 mg/3wk		2.56(0.31,23.11)	2.64(0.41,20.73)
IM TE 250 mg/4 wk		1.97(0.18,28.25)	2.08(0.19,24.77)
IM TE 300 mg/3wk		0.87(0.12,6.50)	0.90(0.14,5.18)
IM TE 50-400 mg/wk		0.76(0.02,24.24)	0.83(0.02,28.12)
IM TC 200 mg/2 wk		6.06(0.65,66.60)	6.10(0.83,69.47)
Gel 1% 100 mg/d	Gel 1% 50 mg/d	1.01(0.27,3.64)	0.98(0.35,2.72)
Gel 1.62% 40.5 mg/d		9.73(1.26,160.90)	9.46(1.45,178.70)
Gel 2% 60 mg/d		1.84(0.51,6.67)	1.82(0.68,5.04)
Oral TU 160 mg/d		0.94(0.25,3.46)	0.94(0.34,2.68)
Oral TU 120-160 mg/d		0.60(0.01,16.04)	0.56(0.01,13.14)
IM TU 1000 mg/12 wk		0.55(0.16,1.90)	0.56(0.18,1.69)
IM TE 125 mg/wk		7.20(0.82,73.89)	7.15(1.01,75.68)
IM TE 150 mg/2 wk		0.89(0.05,13.11)	0.82(0.04,12.23)
IM TE 200 mg/2wk		2.94(0.53,18.41)	2.93(0.61,15.73)
IM TE 250 mg/3wk		2.20(0.30,17.34)	2.23(0.36,17.15)
IM TE 250 mg/4 wk		1.69(0.17,22.80)	1.75(0.17,20.65)
IM TE 300 mg/3wk		0.75(0.11,4.89)	0.76(0.13,4.18)
IM TE 50-400 mg/wk		0.63(0.01,19.41)	0.70(0.02,23.40)
IM TC 200 mg/2 wk		5.18(0.59,53.21)	5.16(0.73,55.76)
Gel 1.62% 40.5 mg/d	Gel 1% 100 mg/d	9.86(1.10,175.60)	9.72(1.42,190.30)
Gel 2% 60 mg/d		1.84(0.42,8.24)	1.86(0.60,5.88)
Oral TU 160 mg/d		0.94(0.20,4.23)	0.96(0.30,3.06)
Oral TU 120-160 mg/d		0.61(0.01,16.76)	0.57(0.01,14.01)
IM TU 1000 mg/12 wk		0.55(0.13,2.37)	0.57(0.16,1.93)
IM TE 125 mg/wk		7.17(0.75,81.81)	7.33(0.95,81.33)
IM TE 150 mg/2 wk		0.91(0.04,14.61)	0.83(0.04,13.17)
IM TE 200 mg/2wk		2.96(0.46,21.06)	2.99(0.57,17.59)
IM TE 250 mg/3wk		2.23(0.25,20.18)	2.28(0.33,18.50)
IM TE 250 mg/4 wk		1.71(0.15,24.04)	1.79(0.16,22.45)
IM TE 300 mg/3wk		0.75(0.10,5.83)	0.77(0.12,4.67)
IM TE 50-400 mg/wk		0.64(0.01,21.71)	0.71(0.02,24.62)

IM TC 200 mg/2 wk		5.23(0.54,58.01)	5.27(0.69,60.71)
Gel 2% 60 mg/d	Gel 1.62% 40.5 mg/d	0.19(0.01,1.65)	0.19(0.01,1.32)
Oral TU 160 mg/d		0.10(0.01,0.83)	0.10(0.00,0.71)
Oral TU 120-160 mg/d		0.05(0.00,2.49)	0.05(0.00,2.11)
IM TU 1000 mg/12 wk		0.06(0.00,0.47)	0.06(0.00,0.44)
IM TE 125 mg/wk		0.74(0.02,13.90)	0.73(0.02,12.94)
IM TE 150 mg/2 wk		0.08(0.00,2.24)	0.08(0.00,2.05)
IM TE 200 mg/2wk		0.30(0.01,3.85)	0.30(0.01,3.41)
IM TE 250 mg/3wk		0.22(0.01,3.65)	0.23(0.01,3.34)
IM TE 250 mg/4 wk		0.17(0.01,4.16)	0.18(0.01,3.67)
IM TE 300 mg/3wk		0.07(0.00,1.03)	0.08(0.00,0.87)
IM TE 50-400 mg/wk		0.06(0.00,3.14)	0.07(0.00,3.48)
IM TC 200 mg/2 wk		0.51(0.02,10.62)	0.53(0.02,10.18)
Oral TU 160 mg/d	Gel 2% 60 mg/d	0.51(0.11,2.24)	0.52(0.16,1.58)
Oral TU 120-160 mg/d		0.32(0.01,9.15)	0.30(0.01,7.35)
IM TU 1000 mg/12 wk		0.30(0.07,1.27)	0.31(0.09,0.99)
IM TE 125 mg/wk		3.93(0.40,43.28)	3.91(0.53,42.17)
IM TE 150 mg/2 wk		0.49(0.02,7.70)	0.45(0.02,7.00)
IM TE 200 mg/2wk		1.60(0.26,11.41)	1.60(0.31,9.19)
IM TE 250 mg/3wk		1.19(0.14,10.88)	1.22(0.18,9.72)
IM TE 250 mg/4 wk		0.93(0.08,13.60)	0.96(0.09,11.70)
IM TE 300 mg/3wk		0.40(0.05,3.06)	0.41(0.06,2.46)
IM TE 50-400 mg/wk		0.35(0.01,11.62)	0.38(0.01,13.23)
IM TC 200 mg/2 wk		2.83(0.30,31.83)	2.83(0.37,32.24)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	0.64(0.01,18.46)	0.59(0.01,14.56)
IM TU 1000 mg/12 wk		0.59(0.14,2.46)	0.59(0.17,2.03)
IM TE 125 mg/wk		7.75(0.81,86.07)	7.58(1.00,85.05)
IM TE 150 mg/2 wk		0.95(0.04,15.09)	0.87(0.04,13.94)
IM TE 200 mg/2wk		3.15(0.50,21.53)	3.10(0.59,18.27)
IM TE 250 mg/3wk		2.34(0.26,22.45)	2.36(0.34,19.29)
IM TE 250 mg/4 wk		1.79(0.16,26.56)	1.86(0.17,23.04)
IM TE 300 mg/3wk		0.79(0.10,6.08)	0.80(0.12,4.84)
IM TE 50-400 mg/wk		0.70(0.02,21.69)	0.74(0.02,26.24)
IM TC 200 mg/2 wk		5.48(0.58,66.53)	5.50(0.70,63.68)
IM TU 1000 mg/12 wk	Oral TU 120-160 mg/d	0.92(0.03,42.33)	1.00(0.04,47.20)
IM TE 125 mg/wk		12.63(0.28,785.90)	13.63(0.35,945.40)
IM TE 150 mg/2 wk		1.45(0.02,132.60)	1.50(0.02,135.60)
IM TE 200 mg/2wk		4.91(0.15,293.90)	5.44(0.17,301.10)
IM TE 250 mg/3wk		3.62(0.09,282.60)	4.13(0.11,266.10)
IM TE 250 mg/4 wk		2.89(0.06,247.30)	3.27(0.07,262.60)
IM TE 300 mg/3wk		1.24(0.03,75.26)	1.37(0.04,78.83)
IM TE 50-400 mg/wk		1.10(0.01,170.80)	1.31(0.01,195.50)
IM TC 200 mg/2 wk		8.83(0.20,628.00)	9.82(0.25,731.80)
IM TE 125 mg/wk	IM TU 1000 mg/12 wk	13.21(1.35,148.00)	12.87(1.61,151.50)
IM TE 150 mg/2 wk		1.62(0.08,25.01)	1.49(0.07,24.72)

IM TE 200 mg/2wk		5.36(0.87,35.65)	5.29(0.94,32.89)
IM TE 250 mg/3wk		3.97(0.54,31.48)	4.01(0.63,31.25)
IM TE 250 mg/4 wk		3.05(0.29,43.16)	3.16(0.28,40.92)
IM TE 300 mg/3wk		1.37(0.18,9.49)	1.36(0.20,8.69)
IM TE 50-400 mg/wk		1.16(0.03,36.05)	1.26(0.03,45.61)
IM TC 200 mg/2 wk		9.36(1.01,103.80)	9.30(1.16,113.00)
IM TE 150 mg/2 wk	IM TE 125 mg/wk	0.12(0.00,3.32)	0.11(0.00,2.85)
IM TE 200 mg/2wk		0.41(0.03,5.66)	0.41(0.03,4.84)
IM TE 250 mg/3wk		0.30(0.02,5.30)	0.31(0.02,4.56)
IM TE 250 mg/4 wk		0.23(0.01,5.19)	0.24(0.01,4.97)
IM TE 300 mg/3wk		0.10(0.01,1.51)	0.10(0.01,1.26)
IM TE 50-400 mg/wk		0.09(0.00,4.41)	0.09(0.00,4.92)
IM TC 200 mg/2 wk		0.70(0.04,13.20)	0.72(0.04,13.61)
IM TE 200 mg/2wk	IM TE 150 mg/2 wk	3.29(0.17,89.26)	3.63(0.18,94.22)
IM TE 250 mg/3wk		2.48(0.10,79.48)	2.75(0.11,84.83)
IM TE 250 mg/4 wk		1.98(0.07,76.59)	2.19(0.07,88.53)
IM TE 300 mg/3wk		0.84(0.04,25.16)	0.92(0.04,25.30)
IM TE 50-400 mg/wk		0.72(0.01,59.92)	0.87(0.01,72.82)
IM TC 200 mg/2 wk		5.90(0.23,192.50)	6.55(0.24,256.10)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	0.75(0.06,8.84)	0.76(0.07,8.52)
IM TE 250 mg/4 wk		0.57(0.04,10.68)	0.60(0.04,9.30)
IM TE 300 mg/3wk		0.25(0.02,2.50)	0.26(0.03,2.21)
IM TE 50-400 mg/wk		0.22(0.00,8.65)	0.24(0.00,9.71)
IM TC 200 mg/2 wk		1.77(0.13,27.17)	1.77(0.15,26.55)
IM TE 250 mg/4 wk	IM TE 250 mg/3wk	0.77(0.04,17.35)	0.78(0.04,15.21)
IM TE 300 mg/3wk		0.34(0.02,4.14)	0.33(0.03,3.68)
IM TE 50-400 mg/wk		0.28(0.00,13.36)	0.31(0.00,14.83)
IM TC 200 mg/2 wk		2.35(0.14,44.09)	2.33(0.16,41.29)
IM TE 300 mg/3wk	IM TE 250 mg/4 wk	0.44(0.02,6.88)	0.43(0.02,6.85)
IM TE 50-400 mg/wk		0.37(0.00,22.03)	0.39(0.00,25.38)
IM TC 200 mg/2 wk		3.16(0.12,63.54)	3.00(0.15,70.15)
IM TE 50-400 mg/wk	IM TE 300 mg/3wk	0.84(0.01,35.23)	0.93(0.02,42.41)
IM TC 200 mg/2 wk		7.05(0.48,111.90)	6.93(0.57,114.60)
IM TC 200 mg/2 wk	IM TE 50-400 mg/wk	8.04(0.16,617.30)	7.56(0.14,564.20)
Residual deviance		44.96 (52 points)	44.97 (52 points)
DIC		220.59	219.9