

Effect of Periodontal Therapy on Glycemic Control in Diabetic Patients: A systematic review and network meta-analysis

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ABSTRACT

Diabetes mellitus and periodontitis are diseases of high prevalence. These two diseases are also related with each other. Periodontal therapies have already become a part of the treatment for glycemic control; however the benefits of different periodontal therapies are unclear. In the first phase of this study, we performed a systematic review of the current randomized controlled trials for the benefits of periodontal therapies. In the second phase, we analyzed the evidence for the benefits of periodontal therapies (serum HbA1c, fructosamine, periodontal pocket depth, clinical attachment level, bleeding on probing, plaque index, gingival index, C-reaction protein, and gingival crevicular fluid volume). In the third phase, we reported safety issues (total withdrawals, withdrawal due to serious adverse effects, serious adverse events and common adverse effects). In general, most included studies were poorly reported. Additional high-quality research studies into benefits of periodontal therapies are needed.

EXECUTIVE SUMMARY

Background: Periodontal therapies have been used widely for treating diabetic patients, but their efficacies on glycemic control are not well established. We evaluated the current evidence for the benefits of periodontal therapies in a systematic review and network meta-analysis.

Methods: We performed a systematic review and network meta-analysis of randomized controlled trials of at least 90 days duration. Eligible studies were identified through an electronic search of MEDLINE, Embase, Cochrane CENTRAL and PubMed. Studies that included adult patients with both diabetes mellitus and periodontitis were included. Primary efficacy outcomes were HbA1c and fructosamine. Secondary efficacy outcomes included periodontal pocket depth, clinical attachment level, bleeding on probing, plaque index, gingival index, C-reaction protein, and gingival crevicular fluid volume. Safety outcomes of interest were total withdrawals, withdrawals due to serious adverse effects, serious adverse events and common adverse effects (acute inflammation, pain, bleeding, loosening of teeth, headache, dizziness, gastrointestinal disturbances, nausea, diarrhea, metallic taste, irritability, thermal sensitivity, and dry mouth). Mean differences and standardized mean differences with standard deviations were calculated for continuous data, and odds ratios with 95% credible intervals were calculated for binary data. Both subgroup analyses and sensitivity analyses were performed.

Results: Fifty-nine articles met the inclusion criteria. Ten of them were companion articles, leaving 49 different trials, which compared 37 different treatments. All included studies were shorter than 1-year duration and were generally poorly reported. Six efficacy outcomes had sufficient data for network meta-analysis.

Compared with control, the standard treatment of scaling and root planning (SRP) had a statistically significant effect on improving serum HbA1c at both 3 months and the end of study. One combination therapy (of 25) showed a significantly better effect than SRP at 3 months.

SRP had a significant effect on all of the periodontal parameters relative to control/no treatment. Compared with SRP, 9 (of 26) and 12 (of 36) therapies were significantly better on improving PPD at 3 months and at end of study respectively. For the outcome of clinical attachment level (CAL), 3 (of 24) and 10 (of 31) therapies were significantly better than SRP at 3 months and at end of study, respectively. One (of 24) and 2 (of 39) therapies showed a significantly better effect than SRP on BOP at 3 months and end of study respectively. One (of 25) and 6 (of 33) therapies were significantly better than SRP on PI at 3 months and at end of study respectively. As for GI, 2 (of 12) therapies were significantly better than SRP at 3 months and no statistical differences were found between any periodontal therapies at end of study.

We found no difference in the risk of withdrawal (includes any reason) between any periodontal therapies and control. Other safety outcomes had insufficient data for network meta-analysis.

Interpretation: The standard periodontal therapy of SRP was associated with both significantly improved serum HbA1c and periodontal outcomes compared to the control/no treatment condition. At 3 months, one combination therapy showed a better effect on HbA1c than SRP; however, the effect was no longer statistically significant at the end of the study. As for periodontal parameters, the use of some, but not all, combination therapies had a significantly better effect than SRP monotherapy. Based on

the limited data of safety outcomes, we found no increased risk of total withdrawal among participants who used periodontal therapy. The quality of included studies was generally low and further high-quality studies are needed to better understand the benefits and harms of periodontal therapies in diabetic patients.

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TABLE OF CONTENTS

ABSTRACT	ii
EXECUTIVE SUMMARY	iii
ACKNOWLEDGEMENTS	vi
TABLE OF CONTENTS	vii
LIST OF TABLES	ix
LIST OF FIGURES	xiii
LIST OF ABBREVIATIONS	xv
CHAPTER 1: INTRODUCTION	1
1.1 DIABETES MELLITUS	1
1.2 PERIODONTITIS	2
1.3 RELATIONSHIP BETWEEN DIABETES MELLITUS AND PERIODONTITIS	3
1.4 PERIODONTAL THERAPY	5
1.4.1 NON-SURGICAL PERIODONTAL THERAPY	5
1.4.2 SURGICAL PERIODONTAL THERAPY	6
1.5 PREVIOUS SYSTEMATIC REVIEWS	7
1.6 PURPOSE OF THE THESIS	8
CHAPTER 2: METHODS	12
2.1 PICO	12
2.1.1 PARTICIPANTS	12
2.1.2 INTERVENTIONS AND CONTROL	13
2.1.3 EFFICACY OUTCOMES---PRIMARY OUTCOMES	13
2.1.4 EFFICACY OUTCOMES---SECONDARY OUTCOMES	15
2.1.5 SAFETY OUTCOMES	20
2.2 SEARCH METHODS	21
2.3 DATA COLLECTION	22
2.3.1 STUDY ELIGIBILITY	22
2.3.2 DATA EXTRACTION	23
2.3.3 RISK OF BIAS	25
2.4 DATA ANALYSIS	27
2.4.1 GLOSSARY OF TERMS FOR NETWORK META-ANALYSIS	28
2.4.2 STATISTICAL ANALYSIS	28
2.4.2.1 EFFICACY OUTCOMES	29
2.4.2.2 SAFETY OUTCOMES	31
2.4.3 COMBINING OF TREATMENTS	32
2.4.4 SENSITIVITY ANALYSIS	33
2.4.5 SUBGROUP ANALYSIS	34
2.4.6 PUBLICATION BIAS	35
CHAPTER 3: RESULTS	36

3.1 DESCRIPTION OF STUDIES	36
3.1.1 INCLUDED STUDIES	36
3.1.2 EXCLUDED STUDIES	43
3.1.3 RISK OF BIAS	44
3.1.4 COMBINING OF TREATMENTS	46
3.2 NETWORK META-ANALYSIS OF EFFICACY OUTCOMES	48
3.2.1 HEMOGLOBIN A1C (HBA1C)	50
3.2.2 FRUCTOSAMINE	78
3.2.3 PERIODONTAL POCKET DEPTH (PPD)	78
3.2.4 CLINICAL ATTACHMENT LEVEL (CAL)	92
3.2.5 BLEEDING ON PROBING (BOP)	105
3.2.6 PLAQUE INDEX (PI)	116
3.2.7 GINGIVAL INDEX (GI)	128
3.2.8 C-REACTIVE PROTEIN (CRP)	137
3.2.9 GINGIVAL CREVICULAR FLUID (GCF) VOLUME	137
3.3 SUBGROUP ANALYSIS	138
3.4 SAFETY OUTCOMES	161
 CHAPTER 4: DISCUSSION	 167
4.1 SUMMARY	167
4.2 CONTEXT	168
4.2.1 PRIMARY OUTCOMES (HEMOGLOBIN A1C)	168
4.2.2 SECONDARY OUTCMES	169
4.2.3 CORRELATION	172
4.3 CLINICAL IMPORTANCE	173
4.4 SENSITIVITY ANALYSIS	174
4.5 SUBGROUP ANALYSIS	177
4.6 MODEL FIT	178
4.7 STRENGTHS AND LIMITATIONS	179
4.8 CONCLUSIONS	180
 REFERENCES	 182
 TABLE OF APPENDIX	
APPENDIX 1 PRISMA CHECKLIST	190
APPENDIX 2 DETAILED LITERATURE SEARCH STRATEGY	193
APPENDIX 3 LIST OF INCLUDED STUDIES	198
APPENDIX 4 LIST OF EXCLUDED STUDIES	204
APPENDIX 5 CHARACTERISTICS OF TRIALS THAT ASSESSED SPECIFIC OUTCOMES	211
APPENDIX 6 RISK OF BIAS ASSESSMENT	236
APPENDIX 7 COMBINING OF TREATMENTS	263
APPENDIX 8 EVALUATION OF NETWORK CONSISTENCY	269
APPENDIX 9 RESULTS FROM FIXED-EFFECTS MODEL	281

LIST OF TABLES

CHAPTER 1

TABLE 1.1: CHARACTERISTICS AND RESULTS OF PREVIOUS SYSTEMATIC REVIEWS EVALUATING BENEFITS OF PERIODONTAL THERAPY	9
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CHAPTER 2

TABLE 2.1: GINGIVAL BLEEDING INDICES	17
TABLE 2.2: GRADING SYSTEM OF SULCUS BLEEDING INDEX (MSBI)	17
TABLE 2.3: CRITERIA FOR THE GI SYSTEM	18
TABLE 2.4: CRITERIA FOR THE MODIFIED GINGIVAL INDEX (MGI)	18
TABLE 2.5: CRITERIA FOR THE PI SYSTEM	19
TABLE 2.6: SUMMARY OF DATA EXTRACTION FORM	24
TABLE 2.7 DIAGRAM LEGENDS FOR INTERPRETATION OF MEAN DIFFERENCE	30
TABLE 2.8 DIAGRAM LEGENDS FOR INTERPRETATION OF MEAN DIFFERENCE (VISUAL REPRESENTATION)	31
TABLE 2.9 DIAGRAM LEGENDS FOR INTERPRETATION OF RELATIVE RISK	32

CHAPTER 3

TABLE 3.1: CHARACTERISTICS OF INCLUDED TRIALS	39
TABLE 3.2: INCLUDED PERIODONTAL THERAPIES	47
TABLE 3.3: SUMMARY OF CHARACTERISTICS FOR EACH EVIDENCE NETWORK	49
TABLE 3.4: HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	51
TABLE 3.5 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	53
TABLE 3.6 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR HBA1C AT 3 MONTHS	54
TABLE 3.7 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH NO INDUSTRY FUNDING AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	57
TABLE 3.8: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED HBA1C AT 3 MONTHS	58
TABLE 3.9 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS AT LOW RISK OF BIAS/UNCLEAR AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	59
TABLE 3.10 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITHOUT LONG TERM USE OF CHX RINSE AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	61
TABLE 3.11 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	63
TABLE 3.12 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	64
TABLE 3.13 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	67
TABLE 3.14 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR HBA1C AT END OF STUDY	68
TABLE 3.15 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH NO INDUSTRY FUNDING AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	70
TABLE 3.16: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED HBA1C AT END OF STUDY	72

TABLE 3.17 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS AT LOW RISK OF BIAS/UNCLEAR AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	73
TABLE 3.18 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITHOUT LONG TERM USE OF CHX RINSE AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	74
TABLE 3.19 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	77
TABLE 3.20 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	79
TABLE 3.21 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	81
TABLE 3.22 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PPD AT 3 MONTHS	82
TABLE 3.23 PPD---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	84
TABLE 3.24 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	86
TABLE 3.25 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	89
TABLE 3.26 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PPD AT END OF STUDY	90
TABLE 3.27 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	92
TABLE 3.28 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	94
TABLE 3.29 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR CAL AT 3 MONTHS	95
TABLE 3.30 CAL---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	97
TABLE 3.31 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	99
TABLE 3.32 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	102
TABLE 3.33 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR CAL AT END OF STUDY	103
TABLE 3.34 BOP ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	105
TABLE 3.35 BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	107
TABLE 3.36 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR BOP AT 3 MONTHS	108
TABLE 3.37 BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	110
TABLE 3.38 BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	113
TABLE 3.39 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR BOP AT END OF STUDY	114
TABLE 3.40 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	117
TABLE 3.41 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	119
TABLE 3.42 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PI AT 3 MONTHS	120

TABLE 3.43 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	122
TABLE 3.44 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	125
TABLE 3.45 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PI AT END OF STUDY	126
TABLE 3.46 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)	129
TABLE 3.47 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	129
TABLE 3.48 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR GI AT 3 MONTHS	130
TABLE 3.49 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)	133
TABLE 3.50 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)	134
TABLE 3.51 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR GI AT END OF STUDY	135
TABLE 3.52 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	139
TABLE 3.53 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	140
TABLE 3.54 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	141
TABLE 3.55 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	143
TABLE 3.56 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	145
TABLE 3.57 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)	146
TABLE 3.58 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH DM 2 (RANDOM-EFFECTS NMA; MEAN±SD)	148
TABLE 3.59 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH DM 2 (RANDOM-EFFECTS NMA; MEAN±SD)	150
TABLE 3.60 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH MIXED DM (RANDOM-EFFECTS NMA; MEAN±SD)	152
TABLE 3.61 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE PPD< 5MM (RANDOM-EFFECTS NMA; MEAN±SD)	153
TABLE 3.62 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY IN PATIENTS WITH BASELINE PPD< 5MM (RANDOM-EFFECTS NMA; MEAN±SD)	154
TABLE 3.63 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE PPD BETWEEN 5-7MM (RANDOM-EFFECTS NMA; MEAN±SD)	156
TABLE 3.64 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C <7% (RANDOM-EFFECTS NMA; MEAN±SD)	157
TABLE 3.65 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C <7% (RANDOM-EFFECTS NMA; MEAN±SD)	158
TABLE 3.66 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C >8% (RANDOM-EFFECTS NMA; MEAN±SD)	159

TABLE 3.67 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C >8% (RANDOM-EFFECTS NMA; MEAN±SD)	161
TABLE 3.68 TOTAL WITHDRAWALS (RANDOM-EFFECTS NMA; RELATIVE RISK ± 95% CREDIBLE INTERVAL)	162

APPENDIX 9

TABLE A9.1: HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (MEAN±SD)	281
TABLE A9.2: HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD)	283
TABLE A9.3: PPD -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (MEAN±SD)	285
TABLE A9.4: PPD -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD)	287
TABLE A9.5: CAL -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (MEAN±SD)	289
TABLE A9.6: CAL -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD)	291
TABLE A9.7: BOP -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (MEAN±SD)	293
TABLE A9.8: BOP-- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD).....	295
TABLE A9.9: PI -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS	297
TABLE A9.10: PI -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD)	299
TABLE A9.11: GI -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (MEAN±SD)	301
TABLE A9.12: GI -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (MEAN±SD)	302
TABLE A9.13: TOTAL WITHDRAWALS (RELATIVE RISK ± 95% CREDIBLE INTERVAL)	303

LIST OF FIGURES

CHAPTER 3

FIGURE 3.1: SELECTION OF STUDIES FOR INCLUSION IN THE SYSTEMATIC REVIEW (PRISMA)	37
FIGURE 3.2: DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON HBA1C AT 3 MONTHS	55
FIGURE 3.3 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS AMONG TRIALS WITH NO INDUSTRY FUNDING	56
FIGURE 3.4: DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON HBA1C AT END OF STUDY	69
FIGURE 3.5 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PPD AT 3 MONTHS	83
FIGURE 3.6 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PPD AT END OF STUDY	91
FIGURE 3.7 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CAL AT 3 MONTHS	96
FIGURE 3.8 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CAL AT END OF STUDY	104
FIGURE 3.9 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON BOP AT 3 MONTHS	109
FIGURE 3.10 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON BOP AT END OF STUDY	115
FIGURE 3.11 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PI AT 3 MONTHS	121
FIGURE 3.12 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PI AT END OF STUDY	127
FIGURE 3.13 EVIDENCE NETWORK FOR GI AT 3 MONTHS	128
FIGURE 3.14 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON GI AT 3 MONTHS	131
FIGURE 3.15 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON GI AT END OF STUDY	136
FIGURE 3.16 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CRP (VERSUS CONTROL/NO TREATMENT)	137
FIGURE 3.17 EVIDENCE NETWORK FOR HBA1C WITH MIXED DM AT END OF STUDY	152
FIGURE 3.18 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS IN PATIENTS WITH BASELINE PPD BETWEEN 5-7MM	156
FIGURE 3.19 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C <7%	157
FIGURE 3.20 EVIDENCE NETWORK FOR HBA1C AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C <7%	158
FIGURE 3.21 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C >8%	159
FIGURE 3.22 EVIDENCE NETWORK FOR HBA1C AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C >8%	160

APPENDIX 8

FIGURE A8.1 HBA1C: BASE CASE (3 MONTHS)	269
FIGURE A8.2 HBA1C: NO INDUSTRY FUNDING (3 MONTHS)	270
FIGURE A8.3 HBA1C: LOW/UNCLEAR RISK OF BIAS (3 MONTHS)	270
FIGURE A8.4 HBA1C: EXCLUDE LONG TERM USR OF CHX RINSE (3 MONTHS)	270
FIGURE A8.5 HBA1C: PARTIAL MOUTH SRP (3 MONTHS)	271
FIGURE A8.6 HBA1C: AGE < 65 YR (3 MONTHS)	271
FIGURE A8.7 HBA1C: TRIALS WITH TYPE 2 DIABETIC PATIENTS (3 MONTHS)	271
FIGURE A8.8 HBA1C: TRIALS WITH BASELINE PPD <5MM (3 MONTHS)	272
FIGURE A8.9 HBA1C: BASE CASE (END OF STUDY)	272
FIGURE A8.10 HBA1C: NO INDUSTRY FUNDING (END OF STUDY)	272
FIGURE A8.11 HBA1C: LOW/UNCLEAR RISK OF BIAS (END OF STUDY)	273
FIGURE A8.12 HBA1C: EXCLUDE LONG TERM USR OF CHX RINSE (END OF STUDY)	273
FIGURE A8.13 HBA1C: PARTIAL MOUTH SRP (END OF STUDY)	273
FIGURE A8.14 HBA1C: AGE < 65 YR (END OF STUDY)	274
FIGURE A8.15 HBA1C: TRIALS WITH TYPE 2 DIABETIC PATIENTS (END OF STUDY)	274
FIGURE A8.16 HBA1C: TRIALS WITH BASELINE PPD <5MM (END OF STUDY)	274
FIGURE A8.17 PPD: BASE CASE (3 MONTHS)	275
FIGURE A8.18 PPD: PARTIAL MOUTH SRP (3 MONTHS)	275
FIGURE A8.19 PPD: AGE < 65 YR (3 MONTHS)	275
FIGURE A8.20 PPD: BASE CASE (END OF STUDY)	276
FIGURE A8.21 PPD: AGE < 65 YR (END OF STUDY)	276
FIGURE A8.22 CAL: BASE CASE (3 MONTHS)	276
FIGURE A8.23 CAL: PARTIAL MOUTH SRP (3 MONTHS)	277
FIGURE A8.24 CAL: AGE < 65 YR (3 MONTHS)	277
FIGURE A8.25 CAL: BASE CASE (END OF STUDY)	277
FIGURE A8.26 CAL: AGE < 65 YR (END OF STUDY)	278
FIGURE A8.27 BOP: BASE CASE (3 MONTHS)	278
FIGURE A8.28 BOP: BASE CASE (END OF STUDY)	278
FIGURE A8.29 PI: BASE CASE (3 MONTHS)	279
FIGURE A8.30 PI: BASE CASE (END OF STUDY)	279
FIGURE A8.31 GI: BASE CASE (3 MONTHS)	279
FIGURE A8.32 GI: BASE CASE (END OF STUDY)	280
FIGURE A8.33 TOTAL WITHDRAWALS	280

LIST OF ABBREVIATIONS

AGE: advanced glycation end-products

AgP: aggressive periodontitis

ALN: Alendronate

AMX: amoxicillin

aPDT: antimicrobial photodynamic therapy

AV: Aloe Vera

AZM: Azithromycin

BOP: bleeding on probing

CAL: clinical attachment level

CHX: chlorhexidine

CLM: clarithromycin

CP: chronic periodontitis

DCCT: Diabetes Control and Complications Trial

DIC: deviance information criterion

DM: diabetes mellitus

Doxy: doxycycline

EO: essential oil

EGF: epidermal growth factor

FPG: fasting plasma glucose

GI: gingival index

GCF: gingival crevicular fluid

HbA1c: Hemoglobin A1C

HPLC: high-performance liquid chromatography

IDDM: insulin dependent diabetes mellitus

IFG: impaired fasting glucose

IFCC: International Federation for Clinical Chemistry

MCID: minimal clinically important difference

MD: mean difference

MTZ: metronidazole

NGSP: National Glycohemoglobin Standardization Program

NIDDM: non-insulin dependent DM

NMA: network meta-analysis model

NSPT: non-surgical periodontal therapy

OGTT: oral glucose tolerance test

OHI: oral hygiene instruction

PI: plaque index

PPD: periodontal pocket depth

SD: standard deviation

SDD: sub dose doxycycline

SMD: standard mean difference

SMV: simvastatin

SPT: surgical periodontal therapy

SRP: scaling and root planning

SZ: satranidazole

TET: tetracycline

UKPDS: United Kingdom Prospective Diabetes Study

CHAPTER 1: INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disease characterized by the body's inadequate production or use of insulin, which leads to an increased concentration of glucose in the blood. The most common types of diabetes are type 1, type 2 and gestational diabetes (diabetes of pregnancy). Definitions of the three types of diabetes given by the World Health Organization (WHO) are listed below [1]:

- Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. The cause of type 1 diabetes is not known and it is not preventable with current knowledge.
- Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) results from the body's ineffective use of insulin. Type 2 diabetes comprises 90% of people with diabetes around the world [2], and is largely the result of excess body weight and physical inactivity.
- Gestational diabetes is hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes, occurring during pregnancy.

The prevalence of diabetes has been increasing globally in recent decades. In 2014, the global prevalence of diabetes was estimated to be 9% with the highest prevalence among Eastern Mediterranean populations (14%) and lowest in European populations (8%) [3]. In Canada, the estimated prevalence was 9.3% in 2015. By 2025, this figure is expected to increase by 44% [4]. This rapid rise in diabetes prevalence is largely driven by risk factors such as lack of physical activity, overweight, and obesity as well as population aging.

Prolonged hyperglycemia of diabetes mellitus can result in a wide range of complications including cardiovascular disease, stroke, renal failure, diabetic foot, and retinopathy. These complications can have a severe impact on patients' quality of life and life expectancy. According to statistics from the Canadian Diabetes Association, diabetic patients are over 3 and 12 times more likely to be hospitalized with cardiovascular and

end-stage renal disease compared to the general population, respectively [5]. The risk of non-traumatic lower limb amputation in people with diabetes is over 20 times higher than the risk in the general population [5]. It was estimated that diabetes is an underlying or contributing cause of one in ten deaths in Canadian adults [6].

Diabetes imposes a large economic burden worldwide. The total estimated cost of diagnosed diabetes in the United States was \$245 billion in 2012[7]. Medical expenditures of people with diagnosed diabetes are approximately 2.3 times higher than estimated in the absence of diabetes [7].

1.2 PERIODONTITIS

Periodontitis is defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament (PDL) and alveolar bone with pocket formation, recession, or both. Once the damage of PDL and alveolar bone has been established, reversible gingivitis transitions into irreversible periodontitis. The clinical feature that distinguishes periodontitis from gingivitis is the presence of clinically detectable attachment loss [8]. With the progress of inflammation, patients experience constant loss of periodontal supporting tissues and may manifest symptoms such as bleeding gums, gingival necrosis, periodontal abscess, loosening of teeth and/or tooth loss.

Periodontitis generally falls into two categories: chronic and aggressive. Chronic periodontitis (CP) occurs mostly in adults and progresses slowly in general. Destruction of periodontal supporting tissue is consistent with local risk factors (i.e. dental plaque, calculus and overhanging restorations etc.). The rate of disease progression can be slowed down by removing local, systemic and extrinsic risk factors. On the other hand, aggressive periodontitis (AgP), which was previously called early-onset periodontitis, often occurs in people under 35 years of age. Significant attachment loss and bone destruction occurs rapidly both clinically and on radiograph. The degree of damage is usually disproportionately severe given the local risk factors. The effect of treatment by removing risk factors is usually not satisfactory [9]. Both chronic and aggressive

periodontitis can be subcategorized into localized and generalized depending on the proportion of sites involved. Localized periodontitis is characterized with less than 30% sites affected while generalized periodontitis has over 30% sites affected.

Periodontitis is a very common disease with a high prevalence world wide, especially in low- and middle-income countries. According to World Health Organization, “Severe periodontal disease, which may result in tooth loss, is found in 15–20% of middle-aged (35-44 years) adults. Globally, about 30% of people aged 65–74 have no natural teeth [10]”. In the United States, 47.2% adults aged 30 years and older had periodontitis in 2009 through to 2010, distributed as 8.7%, 30.0%, and 8.5% with mild, moderate, and severe periodontitis [11]. In developing countries such as China, based on its 2010 Chronic Disease and Risk Factor Surveillance (CCDRFS) survey, only 10% of the subjects had healthy periodontal tissue [12].

Furthermore, periodontitis is costly to treat. The cost of periodontal disease now is the fourth highest cost of all diseases [13] and consumes between 5 and 10% of public health expenditure [14]. Periodontitis has considerable impact on both individuals and society.

1.3 RELATIONSHIP BETWEEN DIABETES MELLITUS AND PERIODONTITIS

The biggest discovery about periodontitis in the last decade is that it is more than a local infectious disease. Beyond destroying periodontal supporting tissues, it also has systematic affects. Accumulating evidence has shown that periodontitis plays a contributory role in many systemic diseases and is a risk factor for cardiovascular disease, respiratory disease, and adverse pregnancy outcomes among other conditions [15]. Of all the associations observed between periodontitis and chronic systemic disease, the bidirectional link between periodontitis and diabetes mellitus is the most consistent [16-18]. Periodontitis has already been suggested as the sixth complication of diabetes mellitus [19].

Patients with diabetes mellitus are more prone to be diagnosed with periodontitis and suffer from severe periodontal symptoms resulting from alveolar bone loss and local infection [20, 21]. Diabetes mellitus has a direct impact on periodontal status. There is a

positive correlation between glucose content of gingival fluid and blood glucose. That is to say, diabetic patients also have increased glucose level in their gingival fluid that may affect metabolism in gingival tissues as well as the microbial profile [22]. Studies have also shown epidermal growth factor (EGF), which plays a role in maintaining oral health, is significantly lower for diabetic patients compared to non-diabetic patients [23]. Diabetes also has an indirect affect on periodontitis through elevated advanced glycation end-product (AGE) levels and oxidant stress in gingival tissues. When blood sugar levels extend beyond the normal range, the initial formation of reversible products of non-enzymatic glycation and oxidation occurs. The most representative product is glycosylated hemoglobin (HbA1c), which is used for clinical detection of glucose control over months. After a series of further molecular rearrangement, irreversible AGEs are formed and circulate throughout the body [24]. In correspondence with increased AGEs, the receptor for AGE (RAGE) also increases. The reaction of AGEs and RAGE will perturb cellular function and result in induction of elevated cellular oxidant stress [25]. Evidence has shown a significant increase in AGEs and oxidants in diabetic periodontal tissues compared with the tissues of non-diabetic patients [26]. It is believed that elevated AGEs in plasma and tissues are associated with the development of diabetic complications and undermine wound healing, leading to more severe tissue destruction [27].

On the other hand, the presence of periodontitis can have a significant impact on metabolic control. One study conducted by SKM Azizul Islam has investigated the associations of periodontitis with insulin resistance, impaired β -cell function and impaired fasting glucose (IFG). Among subjects without diabetes, after adjustment for confounding factors, participants with periodontitis showed a significantly higher prevalence of impaired fasting glucose and lower β -cell function than participants without periodontitis. Participants with and without periodontitis have similar insulin resistance [28]. Another study used diabetic rats models and showed that chronic periodontitis can alter lipid profiles and affect the metabolism of adipose tissue to inflame diabetes [29]. The underlining mechanism may be explained by inflammatory cytokines and mediators associated with periodontitis, such as TNF-alpha, IL-1 and IL-6 [30]. When periodontal infection occurs, bacteria and their virulence factors initiate a local

infection and trigger a local inflammatory response that generates inflammatory cytokines and mediators. Inflammatory cytokines and mediators produced at gingival level could enter blood circulation and disseminate throughout the body. Once reaching the liver, they can stimulate a systemic inflammatory response [31]. It has long been known that elevated inflammatory cytokines and mediators are related to insulin resistance and glycogen synthesis inhibition, which can in turn deteriorate diabetes mellitus [32, 33].

1.4 PERIODONTAL THERAPY

Currently accepted definition of healthy periodontal tissue includes: the absence of inflammation such as redness, swelling, suppuration as well as bleeding; no epithelial attachment and alveolar bone loss; and functional dental implants [34]. The goals of periodontal therapy are to treat diseases of teeth supporting and surrounding tissues, to preserve the natural dentition and implants, and to maintain and improve the health and function of periodontal and peri-implant tissues.

There is a broad range of periodontal therapies, which can be divided into two categories: non-surgical and surgical.

1.4.1 NON-SURGICAL PERIODONTAL THERAPY

Non-surgical periodontal therapy (NSPT) is the most common treatment of gingivitis/periodontitis. It includes personal oral hygiene instruction (i.e. introduce technique of brushing, interdental brush, dental floss, risk factors of periodontal diseases etc.), mechanical cleaning (i.e. supragingival cleaning, scaling and root planning [SRP]) and maintenance.

In order to obtain a long-term positive effect, oral hygiene instruction (OHI) and maintenance should be applied in every patient with periodontal disease. As for the mechanical cleaning, supragingival cleaning is usually sufficient for the treatment of gingivitis. With the formation of periodontitis and deep pockets, SRP will be required for

deep cleaning. In fact, SRP is considered as the mainstay of periodontal therapy for periodontitis.

By means of mechanical removal of bacterial plaque, calculus as well as affected cementum, mechanical cleaning decreases the bacteria load inside the periodontal pockets and reduces inflammation symptoms. This can be achieved by either hand or powered instrumentation or both [35]. However, not all patients or sites respond well to mechanical periodontal therapy. The reduced effectiveness may be explained by a series of factors such as local anatomy, severity of periodontitis, pathogens and hereditary factors [36]. When indicated, extraction of teeth [37], roots, or implants; systemic or local applied antibiotics [38]; and antimicrobial photodynamic therapy may also be utilized as adjunctive therapies to increase the effect of mechanical cleaning.

In summary, NSPT may include:

- Oral hygiene instruction;
- Mechanical cleaning:
 - Supragingival cleaning: main therapy for gingivitis;
 - Scaling and root planning [SRP]: main therapy for periodontitis;
- Maintenance therapy;
- Tooth extraction;
- Antimicrobial therapy: this could be a mono-therapy of one antibiotic or a combination of several antibiotics regardless of the dose and the way of delivering (i.e. local/systemic delivery);
- Antimicrobial photodynamic therapy (aPDT); or
- Any combination of above.

1.4.2 SURGICAL PERIODONTAL THERAPY

Post-treatment evaluations of NSPT usually take place at 3- and 6- months after the therapy. If periodontal tissue is still in poor health status, surgical periodontal therapy (SPT) may be indicated. SPT may involve: 1) resective procedures such as gingivectomy, gingivoplasty and various mucogingival flap procedures which fold the gum back away from the tooth to expose the tooth root surface and remove deposit crusted on the tooth

root surface under direct vision; 2) regeneration procedures including bone replacement grafts, soft tissue grafts, or guided tissue regeneration; or 3) replacement of teeth by dental implants. All SPT procedures are trying to facilitate effective oral hygiene through thoroughly mechanical debridement, restoring dentition and reshaping gingival and/or alveolar bone form.

In summary, SPT may include:

- Gingivectomy;
- Gingivoplasty;
- Mucogingival Surgery;
- Flap surgery;
- Soft tissue grafting;
- Bone grafting;
- Guided tissue regeneration;
- Crown lengthening surgery etc.

1.5 PREVIOUS SYSTEMATIC REVIEWS

Based on the previously described bidirectional relationship between periodontitis and diabetes mellitus, many randomized controlled trials were published evaluating the effect of periodontal therapy on glycemic control in individuals with diabetes mellitus. The results of these randomized controlled trials are not always homogeneous. The reasons for heterogeneity most likely lie in the variation of study population, study design and treatment methods.

In 1999, Taylor [39] conducted the first review reporting the evidence of periodontal therapy and its impact on diabetes. This article reviewed a body of English-language literature and reported on 10 relevant articles. Of these 10 articles, 3 were controlled trials. One of these specifically involving type 2 diabetes provided evidence to support a beneficial effect while the other 2 found no effect. Due to differences in study design, measurement of periodontal status and definition of cases of diabetes, there was insufficient evidence to make a clear cut conclusion. Taylor suggested more rigorous and systematic studies in the future.

To our knowledge, 13 systematic reviews/meta-analyses have been published exploring the effect of periodontal therapies on diabetes since the first review reported by Taylor in 1999 (Table 1.1). In summary, twelve systematic reviews reported meta-analyses and all the comparisons were between periodontal treatments and no treatment/placebo. No network meta-analysis making head to head comparisons has been conducted. Previous results from meta-analyses regarding the benefit of periodontal therapy on glycemic control are not always consistent. Two meta-analyses [40, 51] revealed no significant differences in HbA1c between intervention and control group. On the contrary, 4 meta-analyses [44, 45, 47, and 49] suggested a significant effect of periodontal therapy on HbA1c/FPG improvement. The rest of the meta-analyses did not have clear cut results. Two of them [47, 49] reported the mean difference in HbA1c/FPG was significant at 3-4 months but non-significant at 6 months. Results of the remaining 4 meta-analyses [41, 43, 46 and 52] showed significant reductions in HbA1c; however the significant results were not robust when subject to subgroup/sensitivity analysis.

Previous systematic reviews have many limitations. First, only a few of the reviews conducted a literature search without language limitation [41, 43, 44, 46, and 47] or used a grey literature search for un-published trials [41, 43, 49, and 50]. Instead of searching multiple databases, one update [45] only included articles retrieved from Medline. Second, many systematic reviews had a small number of articles pooled in their quantitative analysis. Of the included studies, low quality is prevalent. Lastly, most of the previous systematic reviews assessed outcomes at the end of the study, which has a potential impact on the results given that different studies have different durations and the effect of periodontal therapies may vary over time.

1.6 PURPOSE OF THE THESIS

In order to better understand the benefits of different periodontal therapies for glycemic control and their changing patterns over time, a comprehensive, rigorous and well-designed systematic review and network meta-analysis is warranted.

TABLE 1.1: CHARACTERISTICS AND RESULTS OF PREVIOUS SYSTEMATIC REVIEWS EVALUATING BENEFITS OF PERIODONTAL THERAPY

Article	AMSTAR score	Literature search	N of articles pooled	Subgroup /sensitivity analysis	Pooled Studies types	Results	Comment
Janket 2005 ^[40]	5/11	MEDLINE, EMBR, Cochrane Register and bibliographies of the published articles (English articles only)	10	Type 2 DM; use of antibiotic	Intervention studies	PT decrease HbA1c level by 0.38% on average, The number increased to 0.66% and 0.71% respectively when restricted to type 2 diabetic patients and if antibiotics were given. None of the effect was statistically significant.	There is a publication date restriction: from 1980 to 2005.
Darré 2008 ^[41]	6/11	Medline, EMBASE, LILACS, The Cochrane Library, Pascal, IADR Abstracts and Current Contents (No language limitation)	9	Exclude one study that is deviated from the overall effect	Controlled trials	The mean reduction in HbA1c with periodontal therapy was significant (0.46, 95% CI: 0.11, 0.82). However, the sensitivity analysis by excluding one study that is deviated from the overall effect showed non-significant result (0.27, 95% CI: -0.01, 0.60).	The author concluded PT could improve glycemic control but the result should be interpreted with caution due to lack of robustness.
Teeuw 2010 ^[42]	3/11	MEDLINE and Cochrane Library (English articles only)	5 (HbA1c) 3 (FPG)	NA	CCT/RCTs	The weighted mean reduction of HbA1c is significant (-0.40%, 95% CI: -0.77%, -0.04%). The significant improvement in glycemic control was not seen in FPG.	The significant improvement should be viewed with caution for lacking of robustness as revealed by the significant heterogeneity (I^2 : 59.5%, $p=0.04$).
Simpson 2010 ^[43]	8/11	Cochrane Oral Health Group's Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, LILACS, ISI Web of Knowledge and ZETOC (No language limitation)	3 (HbA1c) 2 (CAL, PPD, BOP)	use of antibiotic	RCTs	Results showed significant reduction in HbA1c (-0.40% $p=0.04$); however, the comparison was not significant for either subgroup. A significant reduction was found in PPD and BOP for the patients receiving PT, but not in CAL.	Only RCTs with follow up no less than 3 months were eligible for the inclusion criteria.
Sgolastra 2013 ^[44]	8/11	MEDLINE, Cochrane Controlled Clinical Trial Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CINAHL, Science Direct, Thomson Reuters Web of Knowledge and SCOPUS (No language limitation)	5	NA	RCTs	The results showed that periodontal therapy was effective in the reduction of HbA1C (MD=0.65, 95% CI: 0.43, 0.88; $p<0.05$) and FPG (MD=9.04, 95% CI: 2.17, 15.9; $p<0.05$).	They also analyzed outcomes of total cholesterol, triglycerides, high- and low-density lipoprotein cholesterol, no significant difference were found.

Engelbreton 2013 ^[45]	3/11	MEDLINE (English articles only)	9	NA	RCTs	The results indicated a mean treatment effect of -0.36% HbA1c (95% CI: -0.54, -0.19) compared to no periodontal therapy (p<0.0001).	This is an update of the two systematic reviews that were published in 2010.
Article	AMSTAR score	Literature search	N of articles pooled	Subgroup /sensitivity analysis	Pooled Studies types	Results	Comment
Liew 2013 ^[46]	6/11	Cochrane CENTRAL, Medline and EMBASE (No language limitation)	6	use of antibiotic	RCTs	A significant reduction in HbA1c was evident in treatment group (p = 0.037), with an effect size of -0.41% (95% CI: -0.73%, -0.09%). Subgroup analyses showed a significant improvement of HbA1c level when NSPT was applied alone (p=0.002). However, this improvement was not significant with antibiotic use (p=0.734).	This is another update of the two systematic reviews that were published in 2010. Publication bias was significant with Egger's test (p = 0.014) but not with Begg's test (p = 0.06).
Corbella 2013 ^[47]	5/11	MEDLINE, EMBASE and CENTRAL (No language limitation)	15	use of antibiotic	RCTs	The weighted mean difference in HbA1c was -0.38% (p<0.001) at 3-4 months and increased to non-significant -0.31% (p=0.15) at 6 months. The weighted mean difference in FPG was -9.01 mg/dL (p=0.009) at 3-4 months and -13.62 mg/dL (p=0.06) at 6 months. Subgroup analyses in participants treated with NSPT alone versus adjunctive antimicrobials showing a non-significant increase of HbA1c and non-significant decrease of FPG.	Outcomes were assessed at two different times (i.e. 3 months and 6 months).
Sun 2014 ^[48]	5/11	MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (English articles only)	8	NA	Intervention studies	The meta-analysis revealed that periodontal treatment significantly decreased the level of HbA1c at both 3 and 6 months. However, there was a non-significant decrease in the level of FPG.	Outcomes were assessed at two different times (i.e. 3 months and 6 months). Significant heterogeneity was found among the eight studies.
Wang 2014 ^[49]	6/11	PubMed, Embase and Cochrane Library (English articles only)	10 (3 month) 4 (6 month)	NA	RCTs	After the follow up of 3 months, periodontal therapy significantly improved HbA1c level as well as periodontal status (PPD and CAL). The effect on HbA1c attenuated to non-significant at 6 months after intervention.	Periodontal parameters were assessed along with HbA1c.
Mauri-Obradors 2014 ^[50]	6/11	MEDLINE, Cochrane, Database of Abstracts of Reviews of Effects, CINAHL, Science Direct, ISI Web of	No meta-analysis was conducted	NA	RCTs and Non-RCTs	The author concluded that existing published literature is insufficient to support periodontal therapy as a means to reduce HbA1c levels in type 1 diabetic	The search had a limitation of publication date between 1 January 2001 and 31 October

		Knowledge, Google Scholar and Scopus (English articles only)				patients.	2012.
Wang 2014 ^[51]	7/11	Medline, EMBASE and CENTRAL (No report about language limitation)	4	leave-one-out approach	RCTs	Meta-analysis of the included studies revealed no significant differences in HbA1c results between intervention and control group (-0.238, 95% CI: -0.016, 0.140; p=0.217). The direction and magnitude did not change with the exclusion of individual studies.	There is no evidence of heterogeneity among pooled studies (Q-statistic=1.093, I ² =0%, p=0.579).
Article	AMSTAR score	Literature search	N of articles pooled	Subgroup /sensitivity analysis	Pooled Studies types	Results	Comment
Li 2015 ^[52]	7/11	CEMTRAL, Medline, ISI Web of Knowledge and EMBASE (English articles only)	9	Sample size	RCTs	Pooled results showed that intervention group has statistically significant reduction in HbA1c with an effect size of -0.27% (95% CI: -0.46%, -0.07%). Subgroup analysis based on sample size showed inconsistent results. Periodontal intervention with small sample size (n<80) showed a significant improvement of HbA1c level; however this improvement was not significant with large sample size trials.	Heterogeneity across all included studies was moderate (I ² =41.7% p=0.080).

Notes: BOP=bleeding on probing; CAL=clinical attachment level; CCT=controlled clinical trial; HbA1c=hemoglobin A1c; NSPT=non-surgical periodontal therapy; PPD=periodontal pocket depth; PT=periodontal treatment

CHAPTER 2: METHODS

This systematic review was registered in PROSPERO before starting the literature search. The registration number is CRD42015026701. We followed PRISMA checklist for reporting this systematic review (Appendix 1).

2.1 PICO

2.1.1 PARTICIPANTS

Adults (no less than 18 years old) who are diagnosed with both diabetes mellitus (type 1 or type 2) and periodontitis (chronic or aggressive) were the target population for this systematic review. People who were pregnant, had received periodontal therapy within 6 months or had used antibiotics therapy within 3 months from baseline were excluded.

Based on America Diabetes Association (ADA) [53], the criteria for a diagnosis of diabetes are:

- HbA1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Or
- Fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. Or
- 2-h plasma glucose ≥ 200 mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

We analyzed participants as having a diagnosis of type 1 diabetes mellitus if, at the beginning of the study, the individual's disease classification was juvenile-onset diabetes, type 1 or insulin dependent diabetes mellitus (IDDM). If participants were described as

having adult-onset, type 2 or non-insulin dependent diabetes mellitus (NIDDM) we analyzed them of type 2 diabetes mellitus.

Clinical diagnosis of periodontitis is in accordance with the criteria of American Academy of Periodontology: with a ≥ 1 mm mean clinical attachment level (CAL); sites with PD ≥ 4 ; with BOP and/or suppuration and radiographic evidence of bone loss, including slight, moderate, and severe periodontitis [54].

There was no limitation on participants' general health, smoking habit, and diabetes complications.

2.1.2 INTERVENTIONS AND CONTROL

Interventions used periodontal therapy including surgical periodontal therapy (SPT), non-surgical periodontal therapy (NSPT) or a combination of the two.

Controls used a less intensive periodontal therapy including SPT, NSPT or a combination of the two or used placebo / no treatment.

2.1.3 EFFICACY OUTCOMES----- PRIMARY OUTCOMES

The primary outcomes are indicators of blood glycemic control which include:

- The mean change from baseline in HbA1c to at least 90 days post-treatment.
- The mean change from baseline in fructosamine to at least 90 days post-treatment.

HEMOGLOBIN A1C (HbA1c)

A number of different products have been identified as indicators of blood glucose levels. The glycated hemoglobin assay (HbA1c) is a generally accepted indicator. HbA1c is an irreversible complex that forms when glucose binds to hemoglobin. Its percentage is proportional to average blood glucose concentration over the previous four weeks to three months, therefore providing a useful long-term gauge of blood glucose control.

There are various methods to measure HbA1c. Four basic types are used most commonly: immunoassay, ion-exchange high-performance liquid chromatography

(HPLC), boronate affinity HPLC, and enzymatic assays. Immunoassays measure HbA1c using antibodies to recognize the structure of the N-terminal glycated amino acids of the Hb β chain. Ion-exchange HPLC separates hemoglobin species based on charge differences between HbA1c and other hemoglobins. With boronate affinity methods, m-aminophenylboronic acid reacts specifically with the cis-diol groups of glucose bound to hemoglobin. The enzymatic method currently available measures HbA1c by using an enzyme that specifically cleaves the N-terminal valine [55].

Because test results varied among different assays [56], programs were developed to standardize HbA1c measurements. The mostly widely adopted system is that of National Glycohemoglobin Standardization Program (NGSP), which standardizes glycated hemoglobin test results so that values reported by clinical laboratories are comparable to those reported in the two largest clinical trials on the effects of intensive diabetes treatment, namely the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) [57]. Another reference method was developed by the International Federation for Clinical Chemistry (IFCC) [58]. The IFCC reference system produces values that are 1.5–2.0% absolute HbA1c units lower than those measured by the NGSP [59]. To avoid confusion with the widely used NGSP/DCCT/UKPDS units, IFCC numbers are now reported as mmol/mol.

FRUCTOSAMINE

More recently, fructosamine (glycated albumin) has also been used in some articles as a blood glucose indicator. It is a glycated serum protein that acts as a measurement of blood sugar control over two or three weeks rather than months. We include it as a primary outcome because some studies may use this measure either in addition to or as an alternative to HbA1c.

FASTING PLASMA GLUCOSE (FPG)

Some studies using fasting plasma glucose (FPG) measure blood sugar levels. We do not think it is reasonable for this systematic review because evaluations of periodontal

therapy are usually on a monthly basis while FPG reflects blood glucose change within hours and will be heavily influenced by factors such as recent diet and exercise.

2.1.4 EFFICACY OUTCOMES----- SECONDARY OUTCOMES

In this systematic review, periodontal status was measured as pre-planned and described in PROSPERO. The role of the secondary outcomes in this project is to help understand the relationship between periodontal therapy and glycemic control, since it is the improvement in periodontal health that has been postulated to help with DM control in patients with both DM and periodontitis. Several clinical periodontal indexes are included as secondary outcomes:

- Changes in periodontal probing depth (PPD)
- Changes in clinical attachment level (CAL)
- Changes in bleeding on probing (BOP)
- Changes in gingival index (GI)
- Changes in plaque index (PI)
- Change in gingival crevicular fluid (GCF) volume
- Change in C-reactive protein level (CRP)

PERIODONTAL PROBING DEPTH (PPD)

Periodontal probing depth (PPD) is defined as the distance from the base of a sulcus or periodontal pocket to a gingival margin measured in millimeters. It measures the depth of the periodontal pocket and indirectly reflects the alveolar bone destruction. Healthy gingival sulcus has a probing depth range from 1 to 3 mm and it's usually greater than 3 mm in periodontal pockets. Measurement of PPD takes place at six sites per tooth (distofacial, facial, mesiofacial, distolingual, lingual, and mesiolingual) with one reading per site. The record number of each site will be rounded to the nearest full millimeter.

CLINICAL ATTACHMENT LEVEL (CAL)

Clinical attachment level (CAL) is another periodontal index reflecting the degree of alveolar bone damage. It is defined as the distance (in millimeters) from the base of a sulcus or periodontal pocket to the cementoenamel junction (CEJ), which is a fixed point that does not change throughout life.

For the convenience of CAL calculation, 2 clinical parameters are commonly used: PPD and distance from the gingival margin to the CEJ. There are 3 relative positions of gingival margin and CEJ. Different computation formulas are used in different scenarios, namely:

- Gingival margin is apical to the CEJ, which is known as recession.
- The CEJ is at the same level as the gingival margin.
- Gingival margin is coronal to the CEJ.

In the situation of recession, CAL is calculated by PPD plus the distance from gingival margin level. When CEJ is at the same level of gingival margin, CAL equals PPD. In the last scenario, CAL is calculated by subtracting the gingival margin level from the PPD.

BLEEDING ON PROBING (BOP)

Bleeding on probing (BOP) is widely used as an indicator of periodontal inflammation and disease progression. Bleeding can be visible immediately when a site is probed or several seconds later. Many bleeding indices have already been devised [60]. Some simply record BOP as positive or negative [61] whereas others used grading scales in an attempt to assess severity of bleeding (Table 2.1). The most commonly used grading-scale, modified Sulcus Bleeding Index (mSBI), was devised by Mombelli [62] et al in 1987 (Table 2.2)

TABLE 2.1 GINGIVAL BLEEDING INDICES

Index name	Graded response	Time delay (seconds)
Sulcus Bleeding Index (SBI)	Yes (0-5)	Not stated
Modified Sulcus Bleeding Index (mSBI)	Yes (0-3)	Not stated
Gingival Bleeding Index (GBI)	No (yes/no)	10s
Papillary Bleeding Index (PBI)	Yes (0-3/4)	20-30s
Papillary Bleeding Score (PBS)	Yes (0-5)	Not stated
Bleeding Time Index (BTI)	Yes (0-4)	0-30s

TABLE 2.2 GRADING SYSTEM OF SULCUS BLEEDING INDEX (MSBI)

Score	Grading criterion
0	No bleeding when a periodontal probe is passed along the gingival margin adjacent to the implant
1	Isolated bleeding spot visible
2	Blood forms a confluent red line on margin
3	Heavy or profuse bleeding

GINGIVAL INDEX (GI)

Besides BOP, gingival index (GI) is another commonly used scale to describe gingival status. GI was first introduced by Loe and Silness in 1963 [63] with the main purpose to distinguish between the quality of gingiva and the location as related to the four areas making up the total circumference of the marginal gingiva (Table 2.3). Each of the four gingival areas of the tooth is given a score from 0-3 and the average score from the four areas gives the GI for the tooth. The average GI score from each tooth gives the GI for an individual.

TABLE 2.3 CRITERIA FOR THE GI SYSTEM

Score	Grading criterion
0	Normal gingiva
1	Mild inflammation—slight change in color, slight edema; no bleeding on probing
2	Moderate inflammation—redness, edema and glazing; bleeding on probing
3	Severe inflammation—marked redness and edema; ulceration; tendency to spontaneous bleeding

In 1986, Lobene et al [64] introduced a modified gingival index (MGI) resetting the rating for mild and moderate inflammation (Table 2.4). Units as well as calculation of the index are the same as Löe and Silness's GI system.

TABLE 2.4 CRITERIA FOR THE MODIFIED GINGIVAL INDEX (MGI)

Score	Grading criterion
0	Absence of inflammation
1	Mild inflammation or with slight changes in color and texture but not in all portions of gingival marginal or papillary
2	Mild inflammation, such as the preceding criteria, in all portions of gingival marginal or papillary
3	Moderate, bright surface inflammation, erythema, edema and/or hypertrophy of gingival marginal or papillary
4	Severe inflammation: erythema, edema and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion or ulceration.

PLAQUE INDEX (PI)

Plaque index (PI), which is recorded to indicate severity and location of the soft debris aggregates, reflexes a subject's oral hygiene situation. The most commonly used

plaque index system is Silness-Löe index that matches the gingival index [63]. According to their system, PI is scaled from 0 to 3 with oral hygiene go from good to poor (Table 2.5).

TABLE 2.5 CRITERIA FOR THE PI SYSTEM

Score	Grading criterion
0	No plaque in the gingival area
1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth; the plaque may only be recognized by running a probe across the tooth surface
2	Moderate accumulation of soft deposits within the gingival pocket, on the gingival margin and/or adjacent tooth surface, which can be seen with the naked eye
3	Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface

Identical to the calculation of GI, each of the four gingival areas of the tooth is given a score from 0-3 and the average score from the four areas gives the PI for the tooth. PI scores from each tooth will be added up and divided by the number of teeth to give the PI for an individual.

Besides the most frequently used index as described above, some studies may use a much simpler 0/1 score merely based on absence or presence of soft debris on the tooth surface.

GINGIVAL CREVICULAR FLUID (GCF) VOLUME

Gingival crevicular fluid (GCF) is a complex exudate secreted by the gingiva within the crevicular sulcus. It is derived from serum, host cell as well as subgingival pathogens and creates a flushing action and an isolation effect. Under healthy conditions, about 3µL/hour of GCF is released into crevicular sulcus, while GCF volume increases dramatically as inflammation aggravates [65]. Therefore, GCF volume has been proposed

as a monitor of gingival inflammation. It is most commonly measured by placing a calibrated filter paper strip into the gingival sulcus/periodontal pocket for 30 seconds and calculating the volume collected on the paper.

C-REACTIVE PROTEIN (CRP)

C-reactive protein (CRP) is a protein found in blood plasma. Its level has a positive correlation with severity of inflammation. There are three types of CRP assays [66]: conventional CRP (CRP), high sensitivity CRP (hsCRP) and cardiac CRP (cCRP). Conventional CRP assays are typically considered to be clinically significant at levels above 10 mg/L. It is used for evaluation of infection, tissue injury and inflammatory disorders. High sensitivity CRP has a range of measurement extending below the measurement of conventional CRP assays. Its measurement ranges from 1.0 mg/L to 10.0 mg/L. This lower range of measurement expands the indications for the evaluation of conditions expected to be associated with inflammation. Cardiac CRP also has a measurement range that extends below the measurement of conventional CRP assays. It is used to identify individuals at risk for future cardiovascular disease. Both CRP and hsCRP may be reported in the included trials.

2.1.5 SAFETY OUTCOMES

In previous systematic reviews, safety outcomes have not received adequate emphasis. Safety outcomes were also not always well reported in reviewed RCTs.

However, periodontal therapies are mostly invasive. Adverse events such as pain, bleeding, and anxiety have been reported in previous trials. Moreover, with the adjunctive use of antibiotics, adverse effects related to antibiotics should also be taken into consideration.

After consulting with clinician experts and reviewing previous systematic reviews, we have listed the possible adverse events of interest related with periodontal treatments. Although chances of serious adverse effects such as death or symptoms requiring

hospitalization are small, we include a category called “severe adverse events” to capture this type of event. In summary, safety outcomes are categorized as the following:

- Total withdrawals (includes any reason)
- Withdrawals due to adverse event
- Serious adverse events (e.g. events resulting in hospitalization or death)
- Common adverse events
 - Acute inflammation of periodontal tissue
 - Pain
 - Bleeding
 - Loosening of the teeth
 - Headache
 - Dizziness
 - Gastrointestinal disturbances
 - Nausea/Vomiting
 - Diarrhea
 - Metallic taste
 - Irritability
 - Thermal sensitivity
 - Dry mouth

2.2 SEARCH METHODS

In order to identify the relevant literature, the following databases have been searched to the date of 2015 November 5th: PubMed, MDELINe, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). These databases are all accessible from the health science library of the University of Ottawa. Elaborated search strategies were developed for each database under the help of two experienced medical information specialists (B.S. and E.W.). These strategies were composed of both controlled vocabulary (National Library of Medicine’s MeSH/Medical Subject Heading) and keywords (Appendix 2). There was no limitation on language and date of publication.

In addition to implementation of the large databases search, we also searched TRIP database with the following search strategy: (Diabet* OR hyperglycemia OR hyperglycaemia) AND (periodont* OR periodent* OR perident* OR paradont* OR pericement* OR pyorrhea OR pyorrhea OR dental OR oral OR tooth OR teeth OR scaling OR plann* OR planing OR aPDT OR photodynam*). As well, the abstract and citation database of Scopus is used to identify potential relative articles that have cited articles included in this review.

A grey literature search was conducted in Clinicaltrials.gov, University of York--Centre for Reviews and Dissemination, as well as the National Guideline Clearinghouse.

Furthermore, we scanned the reference lists of all included articles as well as previous systematic reviews to avoid missing relevant articles.

Finally, all of the relevant articles gathered from all searches were compiled and de-duplicated in Distiller SR (Evidence Partners based in Ottawa, Canada).

2.3 DATA COLLECTION

2.3.1 STUDY ELIGIBILITY

Following careful de-duplication across records from the various searches, two reviewers (W.L. and J.P.) independently screened the titles and abstracts and recorded eligibility and decision(s) regarding a further screening of the full text. Articles marked as eligible by either reviewer were kept for the second stage of full text screening. Then the same two reviewers read the full texts of all retained articles independently and enrolled or dismissed the studies based on application of inclusion criteria. Disagreements in the second stage were discussed to reach a consensus. Details were summarized using PRISMA flow chart.

2.3.2 DATA EXTRACTION

Before starting data collection for the full study, the data collection strategy was piloted. Both reviewers (W.L. and J.P.) extracted data independently on a sample of 3 articles using a pre-designed data extraction form. Results were compared and all discords were discussed to reach a consensus.

In this stage of data collection, all of the data were collected by one reviewer (W.L.) and checked by the other (J.P.). Discords were discussed and a third person (G.W.) was consulted when agreement could not be reached.

Data extraction forms were pre-designed in Distiller SR and were modified through testing on three articles. There are five forms, which focused on different aspects of the information collected (Table 2.6).

TABLE 2.6 SUMMARY OF DATA EXTRACTION FORM

Form Name	Content
Studies' characteristics	First author; Journal; Year of publication, Country; Trial name and registration number; Type of diabetes; Funding source; Study design (i.e. RCT/split-mouth RCT)
Participants' characteristics	Diagnostic criteria of periodontitis and diabetes mellitus; Inclusion criteria; Exclusion criteria; Baseline participants' characteristics (number of patients randomized in each group, age, gender, diabetes duration, baseline HbA1c, baseline number of teeth and baseline periodontal probing depth); Treatment in each arm
Efficacy outcomes	Name of outcomes; Assessment time; Outcome unit; Mean, Standard deviation /Standard error at different assessment times; Scales used for outcome measurements
Safety outcomes	Name of outcomes; Outcome definition (if provided in article); Number of events or number of patient with event; Number of patient randomized in each group and Number of patient received therapy
Risk of bias	The Cochrane risk of bias tool for randomized controlled trials was used. There are eight domains to be assessed (sequence generation; allocation concealment; blinding of self-reported outcomes; blinding of subjective outcomes; blinding of objective outcomes; incomplete outcome [efficacy]; incomplete outcome [safety]; selective reporting). Based on the pre-specified rules, we gave a judgement for each domain from the choice of low risk of bias, high risk of bias or unclear.

2.3.3 RISK OF BIAS

Assessment of risk of bias is based on Cochrane risk of bias tool and has been adjusted for this systematic review. It contains eight different domains. In each domain, judgment involved the evaluation of foreseen situations, predefined as follows:

Random sequence generation

- Low risk of bias: computer-based sequence generation (mention of blocks alone is not sufficient for rating of “low”); tossing coin and drawing lots etc.
- High risk of bias: alternation is not acceptable for random sequence generation
- Unclear: insufficient information to judge

Allocation concealment

- Low risk of bias: central and pharmacy randomization; use of sequentially numbered opaque envelopes; random assignment by an independent person etc.
- High risk of bias: alternation is not acceptable because investigators are likely to foresee the allocation
- Unclear: insufficient information to judge

Blinding of participants (only applicable for self-report outcomes)

- Low risk of bias: participants are well blinded e.g. using identical placebo or drug containers
- High risk of bias: non-blinded study; participants have delayed treatment or can deduce what treatment they are receiving; when receiving combined treatments with both drug and periodontal treatment, high risk will be judged if either part of treatment is not blinded
- Unclear: insufficient information to judge e.g. no mention about whether patients were blinded; patients were reported blinded but no information about how they

were blinded; study is described as placebo-controlled but no details of blinding i.e. whether placebo (drug/gel) is identical

- N/A: if there are no self-reported outcomes

Blinding of subjective outcome assessment (i.e. PPD, CAL, BOP, PI, and GI)

- Low risk of bias: both patients and clinicians are well blinded such as using identical placebo; assessors are well blinded but patients are not and care is taken to prevent patients revealing their treatment; clinician who provided the treatments is not blinded but the assessor of clinical outcomes is a different person and is blinded
- High risk of bias: the same clinician, who is not well blinded, provides treatment and records clinical parameters; assessor can deduce the treatment groups
- Unclear: clinician who gives the treatment is not blinded and there is insufficient information about whether they used an independent assessor; same person treated and assessed patients but can not judge whether he/she is blinded; patients were not blinded and no further description about whether caution is taken to blind the clinicians
- N/A: if there are no subjective outcomes i.e. no clinical periodontal outcomes

Blinding of objective outcomes (i.e. HbA1c, Fructosamine and GCF volume)

- Low risk: since lack of blinding is unlikely to influence objective outcomes, we will judge it as low risk regardless of blinding
- NA: if there are no objective outcomes

Incomplete outcome ----- efficacy

- Low risk: overall withdrawal rate is less than 20% with no significant difference between groups; Overall withdrawal rate is over 20% and proper imputations are used e.g. intention to treat (ITT)

- High risk: overall withdrawal rate is over 20% and per-protocol analysis or improper imputations (e.g. Last Observation Carry Forward [LOCF]) were used
- Unclear: study did not report randomized number as well as number of withdrawals in each group; Overall withdrawals is reported and is less than 20% but did not break down by groups; Overall withdrawals is over 20% but no information about method of analysis

Incomplete outcome ----- safety

- Low risk: study has no withdrawals due to adverse event; the reasons for withdrawals due to adverse event are accounted for well
- High risk: the reasons for withdrawals due to adverse event are related to the interventions
- Unclear: the reasons for withdrawals due to adverse event are not given or unclear
- N/A: if there is no safety outcome reported or the safety outcomes that we are interested in are not reported

Selective reporting

- Low risk: protocol is available and all outcomes specified in the protocol are well reported; protocol is not available but safety outcomes, numbers of total withdrawals, all pre-specified and important outcomes are reported
- High risk: safety outcomes are not reported; numbers of total withdrawals are not reported or not broken down by groups; statistics are not sufficiently reported (e.g. data needs to be extracted from graphs or no SE/SD reported); secondary outcomes are reported without PPD and CAL
- Unclear: insufficient information to judge

2.4 DATA ANALYSIS

2.4.1 GLOSSARY OF TERMS FOR NETWORK META-ANALYSIS

- Direct comparison: A comparison of two or more interventions made within a study.
- Direct evidence: Evidence on the relative effects of interventions derived entirely from direct comparisons.
- Indirect comparison: A comparison of two interventions via one or more common comparator. For example, the combination of intervention effects from AC and intervention effects from BC studies may (in some situations) be used to learn about the intervention effect AB.
- Indirect evidence: Evidence on the relative effectiveness of two interventions derived entirely from indirect comparisons.
- Mixed evidence: Evidence on the relative effectiveness of two interventions derived from a combination of direct and indirect comparisons.
- Network diagram: A graphical depiction of how each intervention is connected to the others through direct comparisons. Each line, or edge, depicts a direct comparison between two intervention nodes.
- Similarity: A term used to describe the situation in which different sources of direct or indirect evidence are similar with respect to moderators of the intervention effects. There are two types of moderators: (a) clinical similarity refers to similarity in patients' characteristics, interventions, settings, length of follow up, and outcomes measured; (b) methodological similarity refers to aspects of trials associated with the risk of bias.
- Consistency: In case of a closed loop of mixed treatment, where both direct and indirect evidence is available, it is assumed that treatment effect from direct evidence is consistent with the treatment effect from indirect evidence.
- Convergency: It occurs when the inferences do not depend on the initial starting values and the Gibbs Sampler has reached a stationary distribution.

2.4.2 STATISTICAL ANALYSIS

2.4.2.1 Efficacy outcomes

We performed Bayesian mixed-treatment comparison meta-analysis for the efficacy outcomes. Narrative report was used when meta-analysis could not be performed due to lack of data. For outcomes measured using the same scale, the effect size was expressed in terms of the mean difference (MD; between group difference unadjusted for baseline). For outcomes measured using different scales, standardized mean differences (SMDs) were calculated. Since all scales are in the same direction with smaller numbers indicating better oral hygiene, no conversion is needed. The number of participants analyzed in the articles was used in all analyses. Each node in the network represents one kind of periodontal therapy.

For trials that reported outcome data as medians (quartiles), we assumed the mean to be equal to the median and the SD was equal to 1.35 times of the interquartile range (IQR). Based on the handbook of Cochrane [67], estimating the SD based on the range is not recommended. Therefore, articles that reported their outcome data as medians (ranges) were excluded from our analyses for lack of data.

We used WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) to conduct Bayesian network meta-analyses using a normal likelihood model. SRP was chosen as the reference group in the model. Both random- and fixed-effect network meta-analyses were conducted. In the text, all results are derived from the random-effects models. Results of the fixed-effect model are presented in appendix 9. The codes used in our analysis were a modification of codes available on the website of the School of Social and Community Medicine in Bristol University to accommodate continuous outcomes. Non-informative priors were used throughout the analyses. A Markov Chain Monte Carlo method with 20,000 burn-in and further 20,000 simulations and with three chains of different initial values (i.e., 60,000 simulations in total) was used to obtain point estimates, SDs and 95% credible intervals. 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. For both DIC and residual deviance, a lower value indicates a better model fit. Consistency was evaluated where possible by plotting the deviance from the consistency and inconsistency models. Convergence was assessed

through the Gelman-Rubin convergence statistic R, which compares the ratio of the pooled chain variance to the within variance. Once convergence is reached, R=1. Assessment of similarity was conducted by evaluating patient and trial characteristics and performance of subgroup analysis.

For each efficacy outcome, network meta-analyses were analyzed at both three months and end of study. Direct estimates of efficacy were also compared with mixed estimates (direct + indirect) from the network meta-analysis. All network diagrams were constructed using NodeXL.

Pairwise meta-analyses (versus SRP) were undertaken for outcomes with insufficient data for network meta-analysis using Review Manager 5.3. Both random and fixed effects models combining MD/SMD along with associated 95% confidence intervals were reported for each study as well as for summary measures of effect. Cochrane Q and I² measures were also generated to evaluate heterogeneity.

Table 2.7 is the diagram legend for interpretation of mean difference. Table 2.8 is the legend for visual representation. The key for color-coded results tables is as follows: green cells indicate a statistically significant better outcome; 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 and green cells appear grey.

TABLE 2.7 DIAGRAM LEGENDS FOR INTERPRETATION OF MEAN DIFFERENCE

Treatment	1	2	3	4
1	—			
2	Absolute Mean Difference of treatment 2 compared to treatment 1	—		
3	Absolute Mean Difference of treatment 3 compared to treatment 1	Absolute Mean Difference of treatment 3 compared to treatment 2	—	
4	Absolute Mean Difference of treatment 4 compared to treatment 1	Absolute Mean Difference of treatment 4 compared to treatment 2	Absolute Mean Difference of treatment 4 compared to treatment 3	—

TABLE 2.8 DIAGRAM LEGENDS FOR INTERPRETATION OF MEAN DIFFERENCE (VISUAL REPRESENTATION)

Treatment	1	2	3	4
1		Absolute Mean Difference of treatment 1 compared to treatment 2	Absolute Mean Difference of treatment 1 compared to treatment 3	Absolute Mean Difference of treatment 1 compared to treatment 4
2	Absolute Mean Difference of treatment 2 compared to treatment 1		Absolute Mean Difference of treatment 2 compared to treatment 3	Absolute Mean Difference of treatment 2 compared to treatment 4
3	Absolute Mean Difference of treatment 3 compared to treatment 1	Absolute Mean Difference of treatment 3 compared to treatment 2		Absolute Mean Difference of treatment 3 compared to treatment 4
4	Absolute Mean Difference of treatment 4 compared to treatment 1	Absolute Mean Difference of treatment 4 compared to treatment 2	Absolute Mean Difference of treatment 4 compared to treatment 3	

2.4.2.2 Safety outcomes

Bayesian network meta-analyses were performed for safety outcomes. Narrative report was used when there was insufficient data for network meta-analysis.

WinBUGS software was used for data analysis using a binomial likelihood model. SRP was chosen as the reference group in the model. Both fixed- and random-effects network meta-analyses were conducted; assessment of model fit was based on assessment of the DIC and comparison of residual deviance to the number of unconstrained data points. Vague priors were assigned for basic parameters throughout and informative priors were considered for the variance parameter. A Markov Chain Monte Carlo method with 20,000 burn-in and further 20,000 simulations was used to obtain relative risk and 95% credible intervals. Convergence was assessed using Gelman-Rubin statistic R. Continuity corrections were applied to each cell with a zero event count [68]. Table 2.9 is the diagram legend for interpretation of relative risk.

TABLE 2.9 DIAGRAM LEGENDS FOR INTERPRETATION OF RELATIVE RISK

Treatment	1	2	3	4
1	—			
2	Relative Risk of treatment 2 compared to treatment 1	—		
3	Relative Risk of treatment 3 compared to treatment 1	Relative Risk of treatment 3 compared to treatment 2	—	
4	Relative Risk of treatment 4 compared to treatment 1	Relative Risk of treatment 4 compared to treatment 2	Relative Risk of treatment 4 compared to treatment 3	—

2.4.3 COMBINING OF TREATMENTS

It was expected that a large variety of periodontal therapies would be identified. For example, the same antibiotic could be applied either systemically or locally, at different doses and for different periods of time. There are no standard rules for maintenance therapy, which may result in different studies having unique scenarios with respect to maintenance. Furthermore, it is expected that few studies use monotherapy, which leads to a very complex combination of periodontal treatments.

Therefore, in order to find the balance between complex therapy situations and analytical power, we combined periodontal treatments as follows:

First, although studies suggest placebos may relieve disease symptoms, they are biopsychosocial phenomena and rarely cure. “The evidence to date suggests that the therapeutic benefits associated with placebo effects do not alter the pathophysiology of diseases beyond their symptomatic manifestations”[69]. That is to say, a placebo would be expected to have no or negligible effect on outcomes involved in the network. Therefore, in the network meta-analyses, treatments in the form of “SRP + placebo (tablet/ gel/ risen/ or water irrigation)” were classified into the group of “SRP”.

Second, placement of emergency restoration, removal of restoration overhangs and extraction of unsalvageable teeth are preconditions for non-surgical periodontal treatments. It was expected that some trials would report these procedures prior to SRP while others would not. We made an assumption that all of the emergency treatments have been applied ahead of SRP regardless of reporting.

Third, oral hygiene instruction (OHI) was expected in many trials. In previous studies, OHI was usually at a low level. For example, in most cases OHI included instructions of brushing technique, dental floss and interdental toothbrush. Some trials may dispense toothpaste during the study. We considered this low level of OHI do not have interactions with other periodontal treatments such as SRP and/or antibiotics. Therefore, in the network meta-analysis, when OHI was delivered to every participant, we cancelled it out from all of the parallel treatments.

Fourth, antibiotics were expected to be applied in a variety of ways (e.g. systemically or locally; at different doses; and lasting for different periods of time). After consult with a pharmacist (V.S.), we classified the usage of antibiotics with same expected effects into broader categories.

Finally, the purpose of maintenance is to keep periodontal tissues healthy after mechanical treatments. It includes reinstruction of oral hygiene and mechanical cleaning when indicated [70]. There was no standard rule for maintenance. It could either have different contents or be applied with different frequency. In order to feasibly conduct a network meta-analysis, two authors (W.L. and J.P.) divided maintenance into two categories (intensive and non-intensive) based on frequency and subgingival cleaning. Intensive maintenance was characterized by subgingival mechanical cleaning and/or repeated treatments during the follow up. Otherwise, it was considered as non-intensive.

2.4.4 SENSITIVITY ANALYSIS

In order to assess the robustness of the models, sensitivity analyses related to funding source, risk of bias as well as articles' methodology were performed. In all sensitivity analysis, data were analyzed using the random-effects model, unless otherwise stated.

- Influence of the funding source: It has been long known that trials funded by pharmaceutical companies are more likely to have results favoring their products [71]. In this analysis, we included only data from trials that reported 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.

- Influence of bias: In this analysis, we excluded trials that we judged to be at overall high risk of bias in the 4 domains of sequence generation, allocation concealment, blinding for subjective outcomes, and incomplete data addressed for efficacy outcomes.
- Influence of long-term use of chlorhexidine (CHX) rinse: In two articles (Llambés 2012 /2008 / 2005 and Santos 2013), CHX rinse was prescribed for over 2 months. In order to assess the influence of this extreme long-term use of CHX rinse, the 2 studies were excluded in this analysis.
- Influence of SRP finished within 36-72 hours: Traditionally, SRP is divided into 2-4 sessions with a week apart (PMSRP). There is a theory that SRP finished within a short period of time can reduce the risk of cross infection. It is anticipated that some trials had SRP finished within 36-72 hours (FMSRP). In order to assess its influence, trials that performed SRP within 72 hours were excluded in this analysis.

2.4.5 SUBGROUP ANALYSIS

Subgroup analyses were selected a priori in consultation with clinical experts to compare the benefits of periodontal therapy in diabetic patients. The pre-specified subgroups were age ($< v. \geq 65$ yr), type of diabetes (type 1 v. type 2 v. both type 1 and type 2), severity of periodontal disease ($PPD < 5$ mm v. $5\text{mm} \leq PPD < 7\text{mm}$ v. $PPD \geq 7\text{mm}$) [72] and severity of diabetes ($HbA1c < 7\%$ v. $7\% \leq HbA1c < 8\%$ v. $\geq 8\%$) [73].

Patients were divided into different subgroups according to their baseline characteristics. We classified trials as involving patients aged less than 65 years if the upper limit of 95% CI was below 65. We classified trials as involving patients aged 65 years or older if the lower limit of 95% CI was 65 or above. Similarly, a trial was assigned to a severity subgroup if 95% CI fell into its criterion. Assignment of diabetes type was based on the eligibility criteria of each individual trial. For trials that had

subgroup analyses matching ours, original data were used. In all subgroup analyses, data were analyzed using the random-effects model, unless otherwise stated.

2.4.6 PUBLICATION BIAS

Publication bias was assessed using funnel plots. The standard error (SE) for each estimate would be plotted (vertical axis) against the mean difference/standardized mean difference (MD/SMD; horizontal axis). Trials with a smaller SE for the estimate would fall higher on the graph, while estimates with larger SE would be lower on the graph. An asymmetrical appearance of the funnel plot would indicate the potential existence of publication bias.

CHAPTER 3: RESULTS

3.1 DESCRIPTION OF STUDIES

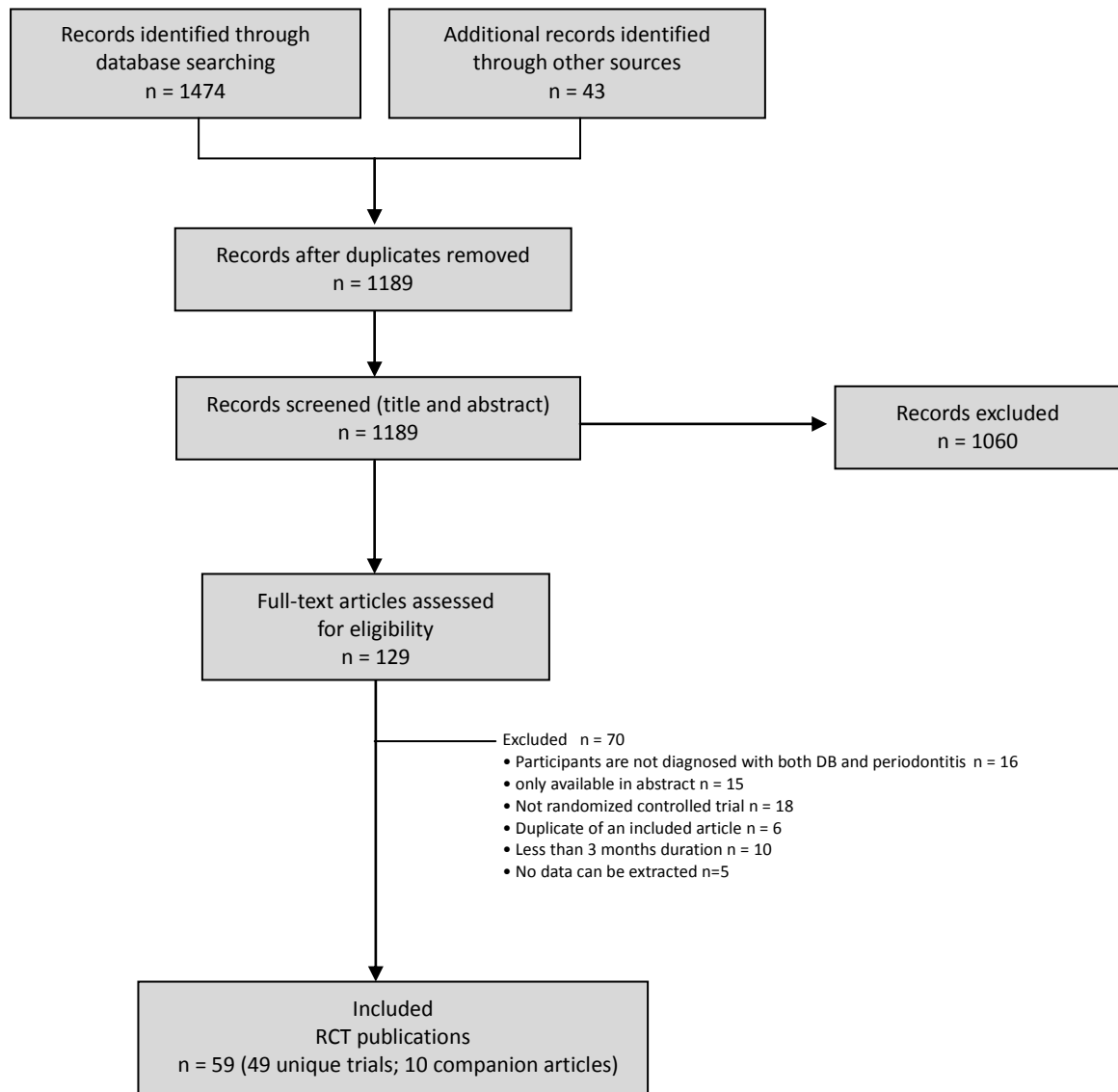
We examined the title and abstracts of 1189 studies, letters and conference abstracts. They were obtained through both an electronic search (PubMed, MDELINE, Embase and CENTRAL) and a hand search. Of these, 1060 were excluded for either not being randomized controlled trials (RCTs) or not meeting the inclusion criteria of study population and/or type of intervention. The full texts of 129 studies were scrutinized in more detail and 70 were excluded after more information became available leaving 59 included in our systematic review (Figure 3.1).

3.1.1 INCLUDED STUDIES

A total of 59 publications met the inclusion criteria of this systematic review. Ten were companion articles leaving 49 different trials evaluating the effect of periodontal therapies on glycemic control and/or periodontal status (Appendix 3). Three studies used split-mouth design (Mendonc 2012; Lima 2004; and Javed 2015). Each patient received two treatments at the same time, which were randomly assigned to either the right or left halves of the dentition. The rest of the studies all used a parallel design.

Except the ones did not report number of study centres, four were multicentre studies (Al-Nowaiser 2014; Engebretson 2013; Mubarak 2010; Katagiri 2008) and 4 were conducted in a single centre (Llambés 2008; Skaleric 2004; Al-Mubarak 2002; Pradeep 2015). Five trials followed patients up to 12 months (Miranda 2014; Santos 2013; Santos 2012; Mubarak 2010; Lima 2004) and 4 trials followed participants for 9 months (Botero 2013; Pradeep 2013; Khader 2010; Agarwal 2012). The remaining 40 trials had a follow up period no more than 6 months. The largest trial (Engebretson 2013) randomized 514 participants while the second largest trial (Mubarak 2010) included 369 participants. The rest of the trials varied in size between 11 and 190 participants.

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



For most of the trials, patients were recruited from outpatient clinics of diabetes/endocrinology or periodontics hospital units, dental clinics and health centres. Four trials recruited from patients referred by their physician to a university periodontal department (Miranda 2014; Santos 2013; Santos 2009; Fu 2006). Macedo 2013 targeted patients by hospital record in a population with a very high incidence of diabetes mellitus. Rocha 2001 drew its participants from home visits and public announcements and Chen 2012 recruited patients from a previous cross-sectional investigation.

No adolescents were recruited in any of the trials. Age ranges varied with the widest range 18 to 80 years old (Al-Mubarak 2002) and the narrowest 50 to 60/35 to 45 years old (Rocha 2001/ Telgi 2013). Three trials included only patients with type 1 DM (Llambés 2012; Skaleric 2004; Lima 2004). Three others trials (Al-Mubarak 2002; Botero 2013; Mubarak 2010) enlisted patients with type 1 or type 2 DM. One trial (Deo 2010) did not provide any information about patients' DM type. The remaining trials included patients with only type 2 DM. Most trials had a near-equal mix of males and females, except Lima 2004 which had nearly all female participants and Javed 2015 which recruited predominantly male participants.

Each study indicated inclusions/exclusions based on the medical condition of each participant. Twenty-three trials recruited patients that had been diagnosed with DM for more than one year. Ten trials restricted to patients with a DM history for over five years (Miranda 2014; Macedo 2013; Lin 2012; Santos 2013; Santos 2012; Santos 2009; O'Connell 2008; Rocha 2001; Mendonca 2012; Rodrigues 2003). Three trials included DM patients with poor glycemic control ($\geq 8\%$) at baseline (O'Connell 2008; Lin 2012; Skaleric 2004). Most trials excluded patients taking antibiotics and having periodontal therapy within a defined prior period. Several trials gave extensive lifestyle data including body mass index (BMI), diet control, smoking, and alcohol consumption.

There were several methods of assessing glycated hemoglobin (HbA1c). Cation-exchange chromatography tests were performed in Rocha 2001. Eleven trials (Miranda 2014; Engebretson 2013; Koromantzios 2011; Santos 2012; Artese 2015; O'Connell 2008; Llambés 2008; Fu 2006; Katagiri 2008; Singh 2008; Elwakeel 2015) used high performance liquid chromatography but with no further details provided. The automated immunoturbidimetric method was used in three trials (Sun 2011; Khader 2010; Gilowski 2012). Engebretson 2011, Kaur 2015 and Gay 2014 used automated affinity chromatography system, latex agglutination inhibition assay and automated boronate affinity assay respectively. The HbA1c test employed was not specified in several studies, although some specified the laboratory used (Rocha 2001; Rodrigues 2003; Tsalikis 2014). Only two studies quoted an HbA1c reference. Raman 2014 standardized its HbA1c results with the DCCT reference while Khader 2010 used the IFCC reference.

One trial had a four-arm design (Mubarak 2010) and 7 trials had a three-arm design (Botero 2013; Li 2011; Chen 2012; Engebretson 2011; Al-Zahrani 2009; Singh 2008; Telgi 2013). All remaining trials used a two-arm design of intervention versus control group. One trial (Gilowski 2012) reported outcome data as medians (quartiles).

Most trials assigned groups to mechanical debridement plus or minus adjunctive antibiotics either systemic or locally applied. The second most commonly used design was comparing one mechanical therapy with another less intensive one or a control/no treatment. In Fu 2006, both intervention and control groups had systemic doxycycline with additional SRP only applied in the intervention group. Two trials (Javed 2015; Koçak 2016) compared mechanical debridement with or without antibacterial photodynamic therapy (aPDT). Another trial (Macedo 2013) also evaluated the effect of aPDT in adjunctive to SRP plus systemic doxycycline.

Table 3.1 gives the general characteristics of the included trials. Characteristics of trials that assessed specific outcomes are listed in Appendix 5.

TABLE 3.1: CHARACTERISTICS OF INCLUDED TRIALS

Author, Year, page	Duration	Groups (No. Randomized)	Age, mean (SD)	Baseline HbA1c mean (SD) (%)	Industry funding	Country	Type of Diabetes	Split mouth
Tsalikis 2014 p.972	6 mo	SRP (35) SRP + Doxy (35)	57.94 (8.22) 62.9 (10)	6.89 (0.60) 6.70 (0.61)	Yes	Greece	Type 2	No
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29) SRP + MTZ + AMX + intensive maintenance (29)	53.7 (8.0) 54.0 (8.2)	8.99 (1.63) 8.53 (1.56)	No	Brazil	Type 2	No
Raman 2014 p.79	3 mo	Intensive OHI (20) SRP + CHX rinse (20)	54.6 (6.2) 57.7 (9.9)	7.6 (1.5) 7.8 (1.5)	No	Malaysia	Type 2	No
Al-Nowaiser 2014 p.1203	6 mo	SRP (38) SRP + Doxy (38)	NR NR	NR NR	NR	Saudi Arabia	Type 2	No
Botero 2013 p.706 (Hincapié 2014 p.89)	9 mo	Supragingival cleaning + AZM (35) SRP (37) SRP + AZM (33)	56.14 (11.32) 58.2 (11.1) 55.9 (12.6)	7.84 (1.92) 7.88 (1.92) 8.05 (2.04)	Mix	Colombia	Mix	No
Macedo 2014 p.881	3 mo	SRP + Doxy + intensive maintenance (15) SRP+ Doxy+ aPDT + intensive maintenance (15)	48.1 (9) 49.4 (6.8)	8.0 (0.93) 8.6 (1.1)	No	Brazil	Type 2	No

Author, Year, page	Duration	Groups (No. Randomized)	Age, mean (SD)	Baseline HbA1c mean (SD) (%)	Industry funding	Country	Type of Diabetes	Split mouth
Engelbrecht 2013 p.2523 (Engelbrecht 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowski 2014 p. 1227)	6 mo	Control/no treatment (257) SRP + CHX rinse + intensive maintenance (257)	57.9 (9.6) 56.7 (10.5)	7.8 (0.60) 7.8 (0.65)	No	United States	Type 2	No
Li 2011 p.285	6 mo	Control/no treatment (25) Supragingival cleaning (19) SRP (22)	61.64 (9.6) 64.21 (5.99) 60.86 (10.22)	8.12 (1.88) 8.15 (1.97) 7.64 (1.77)	No	China	Type 2	No
Bajaj 2012 p. 276	6 mo	SRP (31) SRP + CLM gel (32)	NR NR	NR NR	NR	India	Type 2	No
Llambés 2012 p. e562 (Llambés 2008 p.337; Llambés 2005 p.915)	3 mo	SRP + CHX rinse (30) SRP + CHX rinse + Doxy (30)	33 (8) 38 (10)	NR NR	No	Spain	Type 1	No
Chen 2012 p.435	6 mo	Control/no treatment (44) SRP + non-intensive maintenance (45) SRP + intensive maintenance (45)	63.2 (8.51) 57.91 (11.35) 59.86 (9.48)	7.25 (1.49) 7.29 (1.55) 7.31 (1.23)	No	China	Type 2	No
Lin 2012 p.599	6 mo	SRP (14) SRP + TET gel (14)	59.0 (6.5) 56.6 (7.8)	9.9 (2.2) 9.3 (0.8)	No	China (Taiwan)	Type 2	No
Koromantzios 2011 p. 142 (Koromantzios 2012 p.3; Koromantzios 2014 p. 193)	6 mo	Supragingival cleaning (30) SRP + intensive maintenance (30)	59.42 (9.8) 59.62 (7.95)	7.59 (0.66) 7.87 (0.74)	No	Greece	Type 2	No
Pradeep 2013 p.24	9 mo	SRP (19) SRP + SMV gel (19)	NR NR	6.71 (0.13) 6.66 (0.11)	NR	India	Type 2	No
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19) SRP + CHX (topical) + intensive maintenance (19)	53.9 (10.8) 50.3 (9.5)	10.4 (2.9) 10.0 (2.41)	No	Brazil	Type 2	No

Author, Year, page	Duration	Groups (No. Randomized)	Age, mean (SD)	Baseline HbA1c mean (SD) (%)	Industry funding	Country	Type of Diabetes	Split mouth
Pradeep 2012 p.1322	6 mo	SRP (22) SRP + ALN gel (21)	NR NR	6.85 (0.23) 6.77 (0.19)	NR	India	Type 2	No
Gilowski 2012 p.763	3 mo	SRP (17) SRP + SDD (17)	56.0 (9.0) 57.6 (8.0)	6.2 (6.0, 7.8) 6.7 (6.3, 7.0)	No	Poland	Type 2	No
Mendonca 2012 p. 368 (Bezerra 2014 p.58)	6 mo	SRP + MTZ + AMX + CHX rinse + non-intensive maintenance (21) Flap surgery + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA NA	NA NA	No	Brazil	Type 2	Yes
Moeintaghavi 2012 p.31	3 mo	Control/no treatment (18) SRP (22)	NR NR	8.72 (2.22) 8.15 (1.18)	No	Iran	Type 2	No
Santos 2012 p. 45 (Figueiredo 2014 p. 490)	12 mo	SRP + intensive maintenance (17) FM-SRP + intensive maintenance (17)	51.9 (7.8) 53.1(8.1)	8.9 (2.2) 9.4 (2.5)	No	Brazil	Type 2	No
Engelbrecht 2011 p.624	3 mo	SRP (15) SRP + SDD (15) SRP + Doxy (15)	53.8 (2) 53.2 (3) 54.4 (2)	8.2 (2.0) 7.9 (1.9) 7.6 (2.0)	No	United States	Type 2	No
Khader 2010 p.741	9mo	OHI (29) FM tooth extraction (29)	57.1 (6.9) 55.6 (7.9)	7.73 (0.87) 8.64 (1.24)	No	Jordan	Type 2	No
Deo 2010	6 mo	SRP (inferred 10) SRP + SDD (inferred 10)	NR NR	NR NR	NR	India	NR	No
Mubarak 2010 p.158	12 mo	SRP (98) SRP + SDD (93) SRP + intensive maintenance (75) SRP + SDD + intensive maintenance (80)	51 (6) 48 (5) 47 (4) 43 (6)	9.56 (0.27) 9.14 (0.27) 8.87 (0.29) 9.09 (0.32)	No	Saudi Arabia	Mix	No
Al-Zahrani 2009 p.1568	3 mo	SRP (15) SRP + Doxy (15) SRP + aPDT (15)	53.14 (10.91) 51.42 (6.24) 51.92 (7.28)	8.75 (1.43) 8.42 (1.65) 9.25 (2.71)	No	Saudi Arabia	Type 2	No
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18) FMSRP + intensive maintenance (18)	53.0 (9.2) 52.3 (9.4)	9.2 (1.9) 9.1 (2.1)	NR	Brazil	Type 2	No
Katagiri 2009 p.308	6 mo	Control/no treatment (17) SRP + TET (topical) + intensive maintenance (32)	59.0 (4.8) 60.3 (9.9)	6.9 (0.9) 7.2 (0.9)	Mix	Japan	Type 2	No
O'Connell 2008 p.774	3 mo	SRP + intensive maintenance (15) SRP + Doxy + intensive maintenance (15)	53.5 (13.6) 52.3 (6.3)	10.7 (2.0) 11.8 (1.6)	No	Brazil	Type 2	No

Author, Year, page	Duration	Groups (No. Randomized)	Age, mean (SD)	Baseline HbA1c mean (SD) (%)	Industry funding	Country	Type of Diabetes	Split mouth
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10) SRP + TET (topical) + non-intensive maintenance (10)	41.6 (NR) 42.0 (NR)	9.49 (1.29) 9.11 (0.93)	NR	Slovenia	Type 1	No
Lima 2004 p.648	12 mo	SRP + intensive maintenance (11) SRP + Doxy gel +intensive maintenance (11)	NA NA	NA NA	No	Brazil	Type 1	Yes
Al-Mubarak 2002 p.295	3 mo	SRP (26) SRP + powered subgingival water irrigation (26)	51.5 (14.4) 51.2 (13.6)	8.5 (0.31) 8.060 (0.29)	Yes	United States	Mix	No
Rocha 2001 p.204	6 mo	SRP (20) SRP + ALN (20)	55.0 (3.6) 56.0 (3.5)	13.1 (2.9) 11.9 (3.2)	No	Mexico	Type 2	No
Kaur 2015 p.201	6 mo	Control/no treatment (50) OHI+ SRP+ intensive maintenance (50)	52.94 (6.03) 51.82 (5.85)	7.87 (2.56) 8.17 (2.49)	NR	India	Type 2	No
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15) SRP + AMX + intensive maintenance (15)	NR NR	8.8 (1.8) 9.5 (2.4)	No	Brazil	Type 2	No
Fu 2006 p.32	3 mo	Doxy (23) SRP + Doxy (23)	55.10 (12.71) 53.41 (11.60)	8.22 (2.16) 8.26 (1.49)	NR	China	Type 2	No
Singh 2008 p.38	3 mo	Control/no treatment (15) SRP (15) SRP + Doxy (15)	NR NR NR	8.08 (0.78) 7.93 (0.78) 8.33 (0.71)	No	India	Type 2	No
Sun 2011 p.1569	3 mo	Control/no treatment (75) SRP/flap surgery+ Tinidazole + Ampicillin (82)	54.23 (10.85) 55.13 (11.16)	8.7 (0.65) 8.75 (0.67)	No	China	Type 2	No
Telgi 2013 p.177	3 mo	Control/no treatment (20) CHX rinse (20) SRP + CHX rinse (20)	NR NR NR	7.74 (0.59) 7.56 (0.59) 7.68 (0.63)	NR	India	Type 2	No
Gay 2014 p.673	3 mo	Control/no treatment (77) SRP (77)	54.0 (10.2) 51.5 (9.0)	8.4 (2.0) 9.0 (2.3)	No	United States	Type 2	No
Priyanka 2015 p.42	6 mo	SRP (32) SRP + SZ gel (32)	42.2 (8.2) 40.3 (10.2)	NR NR	NR	India	Type 2	No
Artese 2015 p.1	6 mo	Supragingival cleaning (12) SRP (12)	54.4 (5.8) 52.0 (3.3)	NR NR	No	Brazil	Type 2	No
Gaikwad 2013 p.79	3 mo	SRP (25) SRP + Doxy (25)	NR NR	8.06 (1.10) 8.38 (0.89)	NR	India	Type 2	No
Elwakeel 2015 p.721	6 mo	SRP (NR) SRP + Omega 3 + aspirin (NR)	NR NR	7.59 (0.33) 7.6 (0.4)	No	Egypt	Type 2	No

Author, Year, page	Duration	Groups (No. Randomized)	Age, mean (SD)	Baseline HbA1c mean (SD) (%)	Industry funding	Country	Type of Diabetes	Split mouth
Pradeep 2015	6 mo	SRP (30) SRP + AV gel (30)	34.76 (5.57) 35.03 (4.78)	NR NR	NR	India	Type 2	No
Alshehri 2015 p.1	3 mo	SRP (30) SRP + EO-based rinse (30)	53.4 (2.1) 54.2 (3.5)	NR NR	No	Saudi Arabia	Type 2	No
Agarwal 2012	9 mo	SRP (32) SRP + AZM gel (31)	NR NR	NR NR	NR	India	Type 2	No
Ardakani 2014 p.1387	3 mo	SRP (15) SRP + TET (topical) (15)	NR NR	6.44 (0.35) 6.48 (0.51)	NR	Iran	Type 2	No
Zhang 2013 p. 272	3mo	Control/no treatment (25) SRP (50)	62.7 (10.7) 60.4 (9.77)	7.38 (1.30) 7.68 (1.22)	No	China	Type 2	No
Koçak 2016	3 mo	SRP (30) SRP + aPDT (30)	53.1 (5.1) 51.7 (5.2)	6.5 (0.6) 6.9 (0.7)	No	Turkey	Type 2	No

3.1.2 EXCLUDED STUDIES

After full text examination, 70 articles were excluded for not meeting inclusion criteria or with no extractable data.

Articles only available in abstract were not included in this systematic review (Chandni 2015; Masi 2014; Chee 2008; Zangeneh 2010; Chee 2006; Kothiwale 2013; Skrepinski 1996; Rodrigues 2002; Ryan 2002; Meyle 2013; Michaelowicz 2012; Lima 2012; Weiser 2013; Ciancio 2000; Palioto 2001).

The following studies were also excluded for not recruiting patients diagnosed with both diabetes mellitus and periodontitis: Cinar 2014 (3 articles written by the same author and published in the same year); Rao 2013; Nassar 2011; Lee 2009; Vergnes 2009; Gonzalez-Jimenez 2008; Kiran 2005; Bali 1999; Raslan 2014; Lopez 2012; Pradeep 2015; Christodoulides 2008; Williams 2001. Madden 2008 included diabetic patients with mild or moderate gingivitis or periodontitis. With regard to outcome reporting, data of patients with periodontitis was not separated from those with gingivitis.

Eighteen studies were not designed as randomized controlled trials: Saengtipbovorn 2015; Saengtipbovorn 2014; Vechis-Bon 1989; Albrecht 1988; Grossi 1996; Promsudthi 2005; Bharti 2013; Debnath 2015; Yin 2008; Poletto 2014; Yamashina 2013; Altamash

2015; Correa 2008; Auyeung 2012; Chen 2010; Acharya 2015; Kumar 2015; Bay 1974. Of these non-RCTs, the most commonly used design was that of the interrupted time series study (“before and after” treatment study). Besides this, 2 trials (Saengtipbovorn 2015; Saengtipbovorn 2014) defined themselves as quasi-experimental studies. Four studies (Promsudthi 2005; Bharti 2013; Yamashina 2013; Kumar 2015) incorrectly allocated their patients by placing whoever refused to participate into the control group. One study (Chen 2010) was an observational study.

Ten articles followed up patients for fewer than 90 days: Gokhale 2013; Aldridge 1995; Rosenberg 2015; Obradović 2011; Obradovic 2012; Gadagi 2013; Kesic 2013; Esteghamati 2006; Elavarasu 2015; Matsumoto 2008.

Six articles were duplications. Except for Nassar 2011, the remaining 5 (Al-Nowaiser 2014; Llambés 2012; Engebretson 2013; Novaes 2014; Kaur 2015) were all duplications of included studies without providing additional information.

Two randomized controlled trials were excluded due to incomplete outcome data. Grossi 1997 had a five parallel group design and randomized a total population of 113; however, this study did not report the number of patients randomized in each group. The other study (Javed 2015) was a split-mouth study that had NSPT (non-surgical periodontal therapy) applied in both test and control sites without indicating what kind of NSPT. Also, baseline characteristics were only available for each patient regardless of the test and control sites. Moreover, all results were reported using mean (range), which makes SD/SE calculation unreliable. (Appendix 4)

3.1.3 RISK OF BIAS

Randomization was used in all the included trials. Adequate description of sequence generation was unavailable in 19 trials. Of the rest that provided adequate information, 29 used acceptable methods such as computerized generation, drawing lots and tossing a coin [67]. Only one trial (Mubarak 2010) was judged as at high risk for sequentially allocating their patients into four test groups.

Concealment of allocation was adequately described in 11 trials. Of these, two (Mubarak 2010; Llambés 2012/2008/2005) were judged as at high risk of bias for

allocation being foreseen or breaking concealment. A judgement of unclear for lacking information was given to 38 trials.

Safety outcomes were all patient self-appraised. More than half of the trials (28 trials) did not report anything about safety. Of the 21 trials that reported safety outcomes, 5 (Miranda 2014; Santos 2013; Gilowski 2012; Engebretson 2011; Pradeep 2015) had their patients sufficiently blinded and 7 (Botero 2013/Hincapié 2014; Engebretson 2013; Chen 2012; Mendonc 2012; Santos 2012; Al-Zahrani 2009; Santos 2009) had their patients insufficiently blinded or un-blinded. The rest of the trials had no information about blinding of patients.

Blinding of the clinical operator was not described or insufficiently described in 27 trials. There were three trials did not have periodontal clinical outcomes. Thirteen trials used identical placebo and/or clinical assessor(s) other than treatment provider(s). Six trials did not blind their assessors or assessors could deduce patients' treatment allocation based on the information from the texts. For example, Telgi 2013 mentioned that long term use of CHX rinse could stain the tooth or tongue surfaces, examiner may deduce whether patients were in control group or not.

All included trials had their primary outcomes (i.e. objective outcomes) analyzed by laboratories. Since the objective outcomes are less likely to be influenced by lacking of blinding, we marked them all as being at low risk of bias.

A clear description of withdrawals and method of analysis was given in 37 trials. Fifteen trials followed all participants with no dropouts and 18 trials lost less than 20% of their participants. The remaining 4 trials were at high risk for having a completion rate of less than 80% and using improper statistical analysis (i.e. per-protocol analysis or LOCF).

Twenty-six trials could be assessed in the domain of incomplete outcome [safety]. These include 21 trials that reported patient self-appraised safety outcomes and 5 more trials with information about total withdrawals. Out of the 26 trials, 11 trials had no withdrawals and were judged as being at low risk of bias for incomplete data addressing safety outcomes. One trial (Chen 2012) was also judged as being at low risk of bias for adequate description of the reasons for withdrawals. The rest of the trial reports lacking in information about reasons for withdrawals.

No protocol was found for all included trials. Twelve trials reported all pre-specified outcomes including adverse events in their methods section. Thirty-five trials were judged as high risk in selective reporting for not reporting safety outcomes or insufficient reporting of statistic data. Two trials were marked as unclear. The first one (Bajaj 2012) did not pre-specify outcomes in the methods section and the second one (Engebretson 2011) stated that clinical outcomes would be reported elsewhere but we were unable to find this report.

Details of the results of the risk of bias assessment can be found in Appendix 6.

3.1.4 COMBINING OF TREATMENTS

As expected, we came across a large variety of periodontal therapies. In order to reach the balance between complex therapy situations and analytical power, we combined periodontal treatments as described in the methods chapter. Appendix 7 shows all the details.

With the exception of Raman 2014, which described an intensive OHI protocol, OHI in other studies was at a relatively low level. Therefore, we maintained “intensive OHI” in Raman 2014 and cancelled OHI out from all of the parallel treatments in other studies.

After combining, we included 37 different therapies in total and Table 3.2 shows the details.

TABLE 3.2: INCLUDED PERIODONTAL THERAPIES

SRP	SRP + Omega 3 + aspirin
Control	SRP + powered subgingival water irrigation
OHI	SRP + aPDT
Intensive OHI	SRP+ Doxy+ aPDT
FM tooth extraction	SRP/flap surgery+ Tinidazole + Ampicillin
Supragingival cleaning	CHX rinse
Supragingival cleaning + AZM	SRP + CHX rinse
Doxy	SRP + SZ gel
SRP + SDD	SRP + AV gel
SRP + Doxy	SRP + AZM gel
SRP + AZM	SRP + ALN gel
SRP + ALN	SRP + SMV gel
SRP + intensive maintenance	SRP + CLM gel
SRP + non-intensive maintenance	SRP + TET (topical)
OHI+ SRP+ intensive maintenance	SRP + TET (topical) + intensive maintenance
SRP + SDD + intensive maintenance	SRP + TET (topical) + non-intensive maintenance
SRP + Doxy+ intensive maintenance	SRP + CHX rinse + intensive maintenance
SRP + AMX+ intensive maintenance	SRP + CHX rinse + Doxy
SRP + MTZ + AMX + intensive maintenance	

3.2 NETWORK META-ANALYSIS OF EFFICACY OUTCOMES

Three outcomes (i.e. fructosamine, CRP and GCF volume) could not be included in network meta-analysis due to lack of data. We performed network meta-analyses for six outcomes: HbA1c, PPD, CAL, BOP, GI, and PI. The effect size for HbA1c, PPD and CAL were expressed in terms of the mean difference (MD; between group difference unadjusted for baseline). For outcomes measured using different scales (i.e. BOP, PI and GI), standardized mean differences (SMDs) were calculated.

The number of participants ranged from 1404 to 2715 and involved up to 39 trials and 56 treatment comparisons. Most trials had two parallel treatment groups.

Publication bias could not be assessed for all network meta-analyses due to lack of data. Table 3.3 is the summary of characteristics for each evidence network.

TABLE 3.3: SUMMARY OF CHARACTERISTICS FOR EACH EVIDENCE NETWORK

	HbA1c		PPD		CAL		BOP		PI		GI	
Characteristic	3 mo	End of study	3 mo	End of study	3 mo	End of study	3 mo	End of study	3 mo	End of study	3 mo	End of study
No. of trials	33	35	32	39	30	35	26	30	31	35	13	14
No. of treatment	25	30	26	36	24	31	24	29	25	33	12	16
No. of participants	2660	2711	2519	2715	2452	2597	2308	2430	2496	2610	1404	1464
No. of comparisons	45	54	42	56	38	50	32	43	41	52	17	23
No. of 2-arm trials	27	27	27	32	26	29	23	25	26	28	11	11
No. of multi-arm trials	6	8	5	7	4	6	3	5	5	7	2	3
HbA1c: Hemoglobin A1C; PPD: periodontal pocket depth; CAL: clinical attachment level; BOP: bleeding on porbing; PI: plaque index; GI: gingival index												

3.2.1 HbA1c

Thirty-eight trials reported change in HbA1c as an outcome. Thirty-three and 35 trials contributed respectively to the evidence network at the time point of 3 months and end of study. Most trials measured HbA1c by high-performance liquid chromatography. Others used turbid metric inhibition immunoassay, photometric systems or cation-exchange etc.

3 months

The evidence network for HbA1c at 3 months included 33 trials, 2660 participants and 25 treatments, providing 45 comparisons based on 27 trials with 2 arms and 6 trials with 3 arms. Five trials reporting HbA1c were excluded from this network meta-analysis for one of the following reasons: did not provide data at 3 months (Artese 2015; Rocha 2001); compared FMSRP with PMSRP (Santos 2012; Santos 2009); or treatments were not connected to the network (Khader 2010). There was no evidence of inconsistency in the network (Figure A8.1).

Compared to control/no treatment, SRP was associated with significantly lower serum HbA1c levels (mean difference was -0.34%; 95% CI: -0.64% to -0.04%). Only “SRP plus systemic doxycycline, aPDT and intensive maintenance” showed significantly lowered HbA1c (i.e., improved outcome) compared to the monotherapy of SRP (mean difference was -1.96%; 95% CI: -3.83% to -0.13%). Comparisons between other periodontal therapies and SRP were non-significant (Table 3.4-3.5).

In the direct evidence (Figure 3.2), several treatments appeared to have significantly better effects (lower HbA1c) than SRP; however, these effects were not conserved in the random-effects network meta-analysis model that incorporated indirect evidence. In the fixed effects model, these treatments did show significant effects and SRP plus CHX rinse also appeared to be significant which is inconsistent with both direct evidence and the results from the random-effects model. Based on DIC and total residual deviance, the random-effects model was considered to be a better fit (Table 3.6).

TABLE 3.4 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.34* (0.15)	—								
3	0.23 (0.52)	-0.11 (0.50)	—							
4	0.22 (0.33)	-0.12 (0.29)	-0.01 (0.54)	—						
5	-0.36 (0.44)	-0.70 (0.45)	-0.59 (0.67)	-0.58 (0.54)	—					
6	0.81 (0.48)	0.47 (0.51)	0.58 (0.71)	0.59 (0.58)	1.17 (0.66)	—				
7	-0.02 (0.48)	-0.36 (0.50)	-0.25 (0.71)	-0.24 (0.58)	0.34 (0.66)	-0.83 (0.68)	—			
8	-0.44 (0.36)	-0.78* (0.33)	-0.67 (0.60)	-0.66 (0.44)	-0.08 (0.55)	-1.25* (0.61)	-0.42 (0.60)	—		
9	-0.16 (0.44)	-0.49 (0.46)	-0.38 (0.68)	-0.37 (0.55)	0.20 (0.62)	-0.96 (0.65)	-0.13 (0.66)	0.29 (0.57)	—	
10	-0.12 (0.25)	-0.46 (0.29)	-0.35 (0.57)	-0.34 (0.41)	0.23 (0.51)	-0.93 (0.54)	-0.10 (0.54)	0.32 (0.44)	0.03 (0.50)	—
11	-0.22 (0.17)	-0.55* (0.21)	-0.44 (0.54)	-0.43 (0.36)	0.14 (0.47)	-1.02 (0.51)	-0.19 (0.45)	0.23 (0.39)	-0.06 (0.47)	-0.09 (0.29)
12	-0.19 (0.47)	-0.53 (0.50)	-0.42 (0.70)	-0.41 (0.58)	0.16 (0.65)	-1.00* (0.48)	-0.17 (0.68)	0.25 (0.60)	-0.04 (0.64)	-0.07 (0.53)
13	0.11 (0.43)	-0.22 (0.45)	-0.11 (0.67)	-0.10 (0.54)	0.47 (0.62)	-0.69 (0.65)	0.14 (0.64)	0.56 (0.56)	0.27 (0.61)	0.24 (0.50)
14	0.28 (0.32)	-0.06 (0.35)	0.05 (0.61)	0.06 (0.46)	0.64 (0.55)	-0.53 (0.58)	0.30 (0.58)	0.72 (0.49)	0.43 (0.54)	0.40 (0.41)
15	-0.14 (0.27)	-0.48 (0.31)	-0.37 (0.58)	-0.36 (0.42)	0.22 (0.52)	-0.95 (0.55)	-0.12 (0.55)	0.30 (0.45)	0.02 (0.51)	-0.01 (0.37)
16	-0.91 (0.55)	-1.24* (0.56)	-1.14 (0.75)	-1.13 (0.63)	-0.55 (0.33)	-1.72* (0.74)	-0.88 (0.74)	-0.46 (0.65)	-0.75 (0.71)	-0.78 (0.60)
17	-1.51 (0.81)	-1.84* (0.81)	-1.73 (0.95)	-1.72* (0.87)	-1.15 (0.67)	-2.31* (0.94)	-1.48 (0.95)	-1.06 (0.87)	-1.35 (0.92)	-1.38 (0.84)
18	-0.01 (0.83)	-0.34 (0.83)	-0.24 (0.97)	-0.23 (0.88)	0.35 (0.70)	-0.82 (0.96)	0.01 (0.96)	0.43 (0.89)	0.15 (0.94)	0.12 (0.86)
19	-1.96* (0.92)	-2.30* (0.93)	-2.19* (1.05)	-2.18* (0.98)	-1.60 (0.81)	-2.77* (1.05)	-1.94 (1.05)	-1.52 (0.98)	-1.81 (1.02)	-1.84 (0.95)
20	-0.02 (0.35)	-0.36 (0.31)	-0.25 (0.59)	-0.24 (0.43)	0.33 (0.54)	-0.83 (0.59)	-0.002 (0.59)	0.42 (0.45)	0.13 (0.56)	0.10 (0.42)
21	0.04 (0.26)	-0.30 (0.22)	-0.19 (0.45)	-0.18 (0.30)	0.40 (0.50)	-0.78 (0.55)	0.06 (0.54)	0.48 (0.40)	0.19 (0.51)	0.16 (0.36)
22	0.01 (0.31)	-0.33 (0.35)	-0.22 (0.61)	-0.21 (0.45)	0.37 (0.54)	-0.80 (0.54)	0.03 (0.57)	0.41 (0.48)	0.16 (0.54)	0.13 (0.40)
23	-0.02 (0.28)	-0.35 (0.32)	-0.24 (0.59)	-0.23 (0.43)	0.34 (0.52)	-0.82 (0.55)	0.01 (0.56)	0.43 (0.46)	0.14 (0.52)	0.11 (0.37)
24	0.23 (0.39)	-0.10 (0.36)	0.01 (0.62)	0.02 (0.47)	0.59 (0.57)	-0.57 (0.62)	0.26 (0.62)	0.68 (0.49)	0.39 (0.59)	0.36 (0.46)
25	0.17 (0.43)	-0.17 (0.40)	-0.06 (0.56)	-0.05 (0.45)	0.53 (0.60)	-0.64 (0.64)	0.19 (0.64)	0.61 (0.52)	0.32 (0.61)	0.29 (0.49)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.02 (0.50)	—								
13	0.33 (0.46)	0.31 (0.64)	—							
14	0.49	0.47	0.16	—						

	(0.36)	(0.57)	(0.54)							
15	0.08 (0.31)	0.06 (0.55)	-0.25 (0.51)	-0.42 (0.42)	—					
16	-0.69 (0.58)	-0.71 (0.73)	-1.02 (0.70)	-1.19 (0.64)	-0.77 (0.61)	—				
17	-1.29 (0.83)	-1.31 (0.93)	-1.62 (0.91)	-1.78* (0.87)	-1.37 (0.85)	-0.60 (0.58)	—			
18	0.21 (0.84)	0.19 (0.95)	-0.12 (0.93)	-0.29 (0.88)	0.13 (0.87)	0.90 (0.62)	1.50 (0.86)	—		
19	-1.74 (0.94)	-1.77 (1.04)	-2.07* (1.02)	-2.24* (0.97)	-1.82 (0.96)	-1.05 (0.73)	-0.45 (0.44)	-1.95* (0.96)	—	
20	0.19 (0.37)	0.17 (0.59)	-0.14 (0.55)	-0.30 (0.47)	0.11 (0.44)	0.88 (0.64)	1.48 (0.87)	-0.02 (0.89)	1.94* (0.98)	—
21	0.25 (0.30)	0.23 (0.54)	-0.08 (0.50)	-0.24 (0.42)	0.17 (0.38)	0.94 (0.60)	1.54 (0.84)	0.044 (0.86)	2.00* (0.95)	0.06 (0.38)
22	0.22 (0.35)	0.20 (0.57)	-0.11 (0.53)	-0.27 (0.45)	0.15 (0.41)	0.92 (0.64)	1.51 (0.87)	0.02 (0.88)	1.97* (0.98)	0.03 (0.46)
23	0.20 (0.32)	0.18 (0.54)	-0.13 (0.51)	-0.29 (0.42)	0.12 (0.39)	0.89 (0.62)	1.49 (0.86)	-0.01 (0.87)	1.94* (0.96)	0.01 (0.44)
24	0.45 (0.42)	0.43 (0.61)	0.12 (0.58)	-0.04 (0.51)	0.37 (0.48)	1.14 (0.66)	1.74 (0.89)	0.24 (0.90)	2.19* (0.99)	0.26 (0.48)
25	0.38 (0.45)	0.36 (0.64)	0.05 (0.60)	-0.11 (0.53)	0.31 (0.50)	1.07 (0.69)	1.67 (0.91)	0.18 (0.92)	2.13* (1.01)	0.19 (0.51)
Treatment	21	22	23	24	25					
21	—									
22	-0.03 (0.41)	—								
23	-0.05 (0.38)	-0.02 (0.42)	—							
24	0.20 (0.43)	0.23 (0.50)	0.25 (0.48)	—						
25	0.13 (0.33)	0.16 (0.53)	0.18 (0.51)	-0.07 (0.54)	—					

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 14. SRP + Omega 3 + aspirin |
| 2. Control/no treatment | 15. SRP + aPDT |
| 3. Intensive OHI | 16. SRP + intensive maintenance |
| 4. CHX rinse | 17. SRP + Doxy+ intensive maintenance |
| 5. Supragingival cleaning | 18. SRP + AMX+ intensive maintenance |
| 6. Supragingival cleaning + AZM | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 7. Doxy | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 8. OHI+ SRP | 21. SRP + CHX rinse |
| 9. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 10. SRP + SDD | 23. SRP + TET (topical) |
| 11. SRP + Doxy | 24. SRP + TET (topical) + intensive maintenance |
| 12. SRP + AZM | 25. SRP + CHX rinse + Doxy |
| 13. SRP + MTZ + AMX | |

**TABLE 3.5 HbA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

T**	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																									
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23																									
24																									
25																									

T: treatment

**Legend:

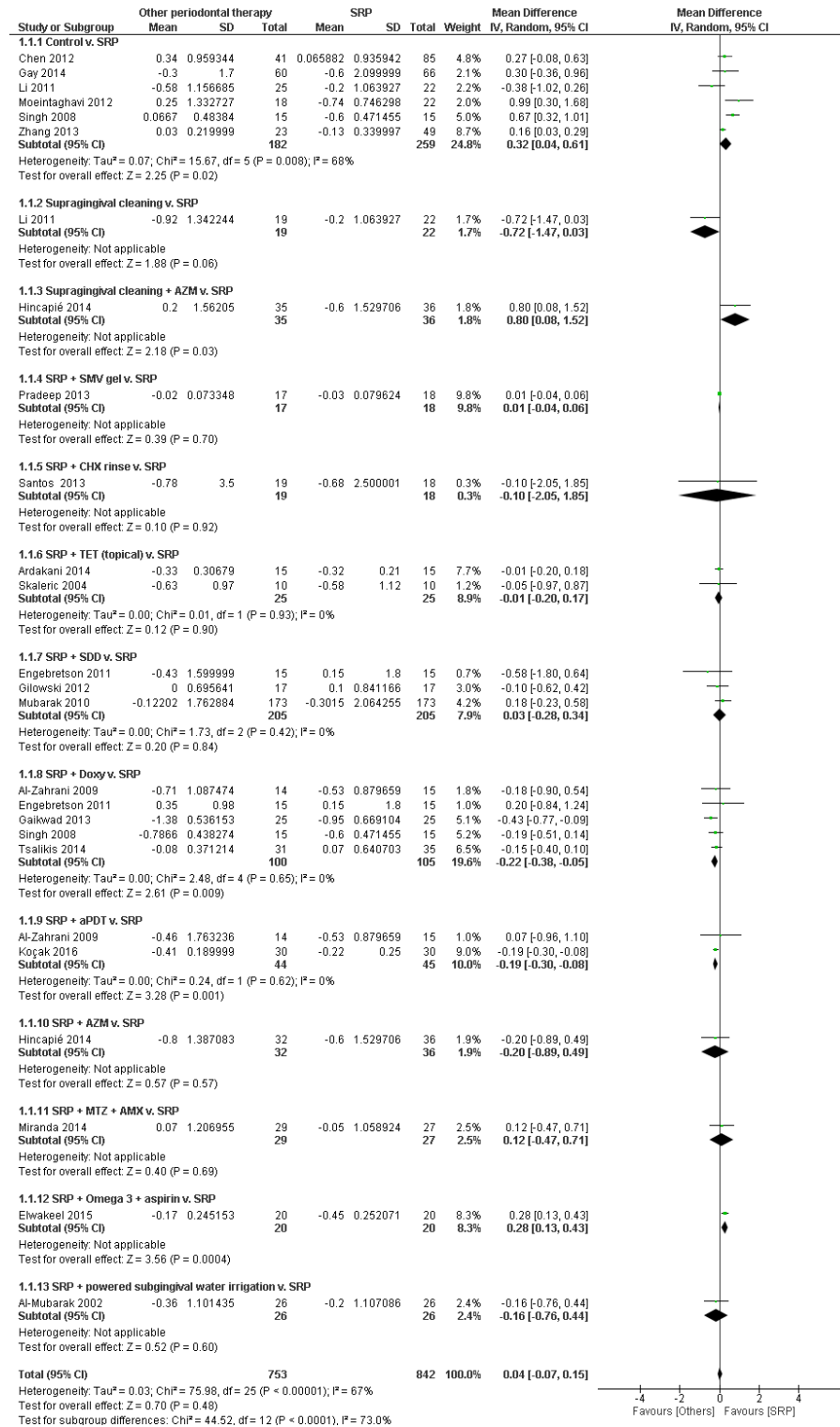
- | | | |
|---|---------------------------------------|---|
| 1. SRP | 10. SRP + SDD | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 2. Control/no treatment | 11. SRP + Doxy | 20. SRP /flap surgery+ Tinidazole + Ampicillin |
| 3. Intensive OHI | 12. SRP + AZM | 21. SRP + CHX rinse |
| 4. CHX rinse | 13. SRP + MTZ + AMX | 22. SRP + SMV gel |
| 5. Supragingival cleaning | 14. SRP + Omega 3 + aspirin | 23. SRP + TET (topical) |
| 6. Supragingival cleaning + AZM | 15. SRP + aPDT | 24. SRP + TET (topical) + intensive maintenance |
| 7. Doxy | 16. SRP + intensive maintenance | 25. SRP + CHX rinse + Doxy |
| 8. OHI+ SRP | 17. SRP + Doxy+ intensive maintenance | |
| 9. SRP + powered subgingival water irrigation | 18. SRP + AMX+ intensive maintenance | |

Green cells indicate a statistically significant improvement of HbA1c; 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 3.6 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR HBA1C AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control//no treatment	SRP	0.32* (0.04, 0.61)	6	68%	0.34* (0.04 to 0.64)	0.24* (0.13 to 0.35)
Supragingival cleaning	SRP	-0.72 (-1.47, 0.03)	1	NA	-0.36 (-1.24 to 0.51)	-0.43 (-1.10 to 0.24)
Supragingival cleaning + AZM	SRP	0.80* (0.08, 1.52)	1	NA	0.81 (-0.15 to 1.75)	0.80* (0.08 to 1.51)
SRP + SMV gel	SRP	0.01 (-0.04, 0.06)	1	NA	0.01 (-0.63 to 0.64)	0.01 (-0.04 to 0.06)
SRP + CHX rinse	SRP	-0.10 (-2.05, 1.85)	1	NA	0.04 (-0.49 to 0.57)	-0.18* (-0.33 to -0.02)
SRP + TET (topical)	SRP	-0.01 (-0.20, 0.17)	2	0%	-0.02 (-0.57 to 0.54)	-0.01 (-0.19 to 0.17)
SRP + SDD	SRP	0.03 (-0.28, 0.34)	3	0%	-0.12 (-0.63 to 0.35)	-0.03 (-0.34 to 0.27)
SRP + Doxy	SRP	-0.22* (-0.38, -0.05)	5	0%	-0.22 (-0.54 to 0.12)	-0.26* (-0.42 to -0.11)
SRP + aPDT	SRP	-0.19* (-0.30, -0.08)	2	0%	-0.14 (-0.67 to 0.42)	-0.19* (-0.30 to -0.08)
SRP + AZM	SRP	-0.20 (-0.89, 0.49)	1	NA	-0.19 (-1.13 to 0.72)	-0.20 (-0.89 to 0.48)
SRP + MTZ + AMX	SRP	0.12 (-0.47, 0.71)	1	NA	0.11 (-0.73 to 0.96)	0.12 (-0.47 to 0.72)
SRP + Omega 3 + aspirin	SRP	0.28* (0.13, 0.43)	1	NA	0.28 (-0.36 to 0.93)	0.28* (0.13 to 0.43)
SRP + powered subgingival water irrigation	SRP	-0.16 (-0.76, 0.44)	1	NA	-0.16 (-1.03 to 0.71)	-0.16 (-0.76, 0.44)
				DIC	-19.598	4.923
				Total residual deviance (Unconstrained data points)	71.11 (72 points)	104.0 (72 points)
Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.						

FIGURE 3.2 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON HBA1C AT 3 MONTHS



SENSITIVITY ANALYSIS

INFLUENCE OF FUNDING

We excluded trials that reported receiving full or partial industry funding. The network involving trials with no industry funding included 21 trials, 1989 patients and 15 treatments, providing 29 comparisons based on 17 trials with 2 arms and 4 trials with 3 arms (Figure 3.3). There was no evidence of inconsistency in the network (Figure A8.2).

The results were congruent with the primary analysis (Table 3.7). SRP still showed a significant effect of reducing HbA1c level as compared to control/no treatment (mean difference was -0.34%; 95% CI: -0.66% to -0.02%). “SRP plus systemic doxycycline, aPDT and intensive maintenance” was still better than SRP monotherapy (mean difference was -1.97%; 95% CI: -3.83% to -0.13%).

FIGURE 3.3 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS AMONG TRIALS WITH NO INDUSTRY FUNDING

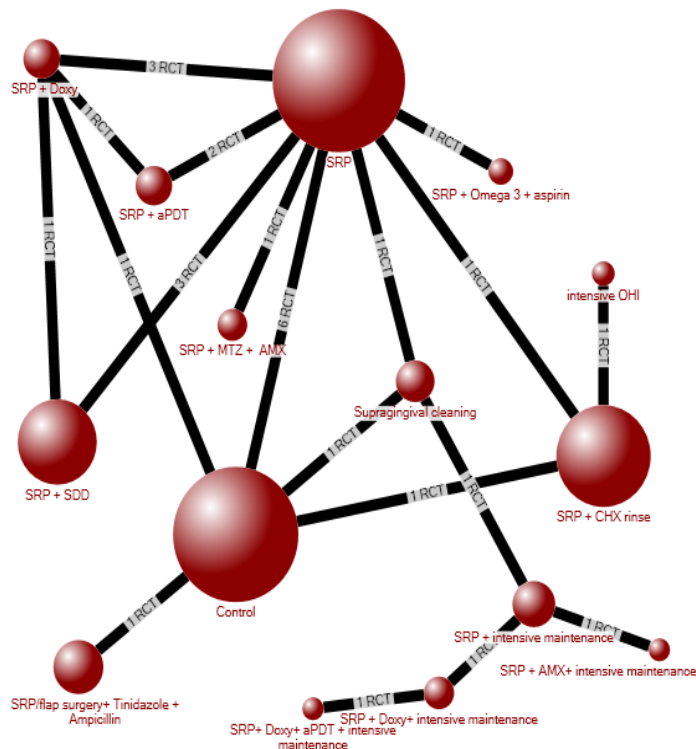


TABLE 3.7 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH NO INDUSTRY FUNDING AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.34* (0.16)	—								
3	0.52 (0.58)	0.18 (0.56)	—							
4	-0.37 (0.45)	-0.70 (0.45)	-0.89 (0.72)	—						
5	-0.12 (0.26)	-0.45 (0.31)	-0.64 (0.63)	0.25 (0.53)	—					
6	-0.17 (0.24)	-0.50 (0.26)	-0.68 (0.62)	0.20 (0.51)	-0.05 (0.33)	—				
7	0.12 (0.45)	-0.22 (0.48)	-0.40 (0.73)	0.49 (0.64)	0.24 (0.52)	0.28 (0.51)	—			
8	0.28 (0.34)	-0.06 (0.38)	-0.24 (0.67)	0.65 (0.57)	0.40 (0.43)	0.44 (0.42)	0.16 (0.56)	—		
9	-0.13 (0.29)	-0.47 (0.33)	-0.65 (0.65)	0.23 (0.53)	-0.02 (0.39)	0.03 (0.35)	-0.25 (0.53)	-0.41 (0.44)	—	
10	-0.92 (0.57)	-1.25* (0.57)	-1.44 (0.80)	-0.55 (0.35)	-0.80 (0.63)	-0.75 (0.61)	-1.04 (0.72)	-1.20 (0.66)	-0.78 (0.64)	—
11	-1.51 (0.82)	-1.84* (0.82)	-2.03* (0.99)	-1.14 (0.69)	-1.39 (0.86)	-1.34 (0.85)	-1.63 (0.93)	-1.79* (0.88)	-1.37 (0.86)	-0.59 (0.60)
12	-0.02 (0.86)	-0.36 (0.86)	-0.54 (1.02)	0.35 (0.73)	0.10 (0.90)	0.14 (0.89)	-0.14 (0.96)	-0.30 (0.92)	0.11 (0.90)	0.90 (0.63)
13	-1.97* (0.94)	-2.30* (0.94)	-2.49* (1.10)	-1.60 (0.84)	-1.85 (0.98)	-1.80 (0.97)	-2.09* (1.04)	-2.25* (1.00)	-1.83 (0.98)	-1.05 (0.76)
14	-0.02 (0.37)	-0.36 (0.33)	-0.54 (0.66)	0.34 (0.57)	0.09 (0.46)	0.14 (0.43)	-0.14 (0.58)	-0.30 (0.51)	0.11 (0.47)	0.89 (0.66)
15	0.32 (0.36)	-0.01 (0.33)	-0.20 (0.46)	0.69 (0.56)	0.44 (0.44)	0.49 (0.42)	0.20 (0.57)	0.04 (0.49)	0.46 (0.46)	1.24 (0.66)
Treatment**	11	12	13	14	15					
11	—									
12	1.49 (0.86)	—								
13	-0.46 (0.46)	-1.94* (0.99)	—							
14	1.48 (0.88)	0.00 (0.92)	1.94 (1.00)	—						
15	1.83* (0.88)	0.34 (0.91)	2.29* (1.00)	0.35 (0.47)	—					

* Statistically significant

**Legend:

- | | | |
|---------------------------|---------------------------------|--|
| 1. SRP | 6. SRP + Doxy | 11. SRP + Doxy + intensive maintenance |
| 2. Control/no treatment | 7. SRP + MTZ + AMX | 12. SRP + AMX + intensive maintenance |
| 3. Intensive OHI | 8. SRP + Omega 3 + aspirin | 13. SRP + Doxy + aPDT + intensive maintenance |
| 4. Supragingival cleaning | 9. SRP + aPDT | 14. SRP/flap surgery + Tinidazole + Ampicillin |
| 5. SRP + SDD | 10. SRP + intensive maintenance | 15. SRP + CHX rinse |

INFLUENCE OF RISK OF BIAS

Of the included trials for this outcome, 9 were excluded in this network meta-analysis for being considered at high overall risk of bias in 4 domains (sequence generation, allocation concealment, blinding for subjective outcomes, and incomplete

data addressed for efficacy outcomes). This leaves for analysis, 24 trials and 19 treatments involving 1829 patients (Table 3.8). There was no evidence of inconsistency in the network (Figure A8.3).

SRP still showed a significant effect of reducing HbA1c level as compared to control/no treatment (mean difference was -0.32%; 95% CI: -0.59% to -0.06%). Two periodontal treatments showed a statistically significant better effect (lower HbA1c) than SRP when studies at high overall risk of bias were excluded. These were “SRP plus systemic doxycycline and intensive maintenance (mean difference was -1.53%; 95% CI: -2.96% to -0.07%)” and “SRP plus systemic doxycycline, aPDT and intensive maintenance (mean difference was -1.99%; 95% CI: -3.62% to -0.37%)”. (Table 3.9)

TABLE 3.8: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED HBA1C AT 3 MONTHS

Trial	Sequence generation	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Tsalikis 2014	Low	Unclear	Unclear	Low	Unclear
Miranda 2014	Low	Low	Low	High	High
Raman 2014	Unclear	Unclear	Unclear	Unclear	Unclear
Hincapié 2014	Low	Low	Unclear	Low	Unclear
Macedo 2013	Low	Unclear	Unclear	Low	Unclear
Engebretson 2013	Unclear	Unclear	Unclear	Low	Unclear
Li 2011	Low	Unclear	Unclear	Unclear	Unclear
Chen 2012	Low	Low	Unclear	Low	Unclear
Koromantzios 2011	Low	Unclear	Low	Low	Unclear
Pradeep 2013	Low	Low	Low	Low	Low
Santos 2013	Low	Unclear	High	Low	High
Gilowski 2012	Unclear	Unclear	Low	Unclear	Unclear
Moeintaghavi 2012	Low	Unclear	Unclear	Low	Unclear
Engebretson 2011	Low	Unclear	N/A	High	High
Mubarak 2010	High	High	Unclear	Unclear	High
Al-Zahrani 2009	Low	Unclear	Unclear	Low	Unclear
Katagiri 2008	Unclear	Unclear	Unclear	Low	Unclear
O'Connell 2008	Unclear	Unclear	Unclear	Unclear	Unclear
Llambés 2008	Unclear	High	Unclear	High	High
Skaleric 2004	Unclear	Unclear	Unclear	Low	Unclear
Al-Mubarak 2002	Unclear	Low	Low	Low	Unclear
Kaur 2015	Low	Unclear	Low	Low	Unclear
Rodrigues	Unclear	Unclear	High	Unclear	High

2003					
Fu 2006	Unclear	Unclear	Unclear	Low	Unclear
Trial	Sequence generation	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Singh 2008	Unclear	Unclear	Unclear	Low	Unclear
Sun 2011	Unclear	Unclear	High	Unclear	High
Telgi 2013	Unclear	Unclear	High	Low	High
Gay 2014	Low	Unclear	Unclear	Low	Unclear
Gaikwad 2013	Unclear	Unclear	Unclear	Unclear	Unclear
Elwakeel 2015	Low	Low	Low	High	High
Ardakani 2014	Unclear	Unclear	Unclear	Unclear	Unclear
Zhang 2013	Low	Unclear	Unclear	Low	Unclear
Koçak 2016	Low	Low	N/A	Low	Low

TABLE 3.9 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS AT LOW RISK OF BIAS/UNCLEAR AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.32* (0.13)	—								
3	0.54 (0.51)	0.22 (0.49)	—							
4	-0.37 (0.41)	-0.69 (0.41)	-0.91 (0.64)	—						
5	0.80 (0.44)	0.48 (0.46)	0.26 (0.68)	1.17 (0.61)	—					
6	-0.10 (0.44)	-0.42 (0.45)	-0.64 (0.67)	0.27 (0.60)	-0.90 (0.63)	—				
7	-0.46 (0.31)	-0.78* (0.28)	-1.00 (0.56)	-0.09 (0.50)	-1.26* (0.54)	-0.36 (0.53)	—			
8	-0.17 (0.39)	-0.49 (0.42)	-0.71 (0.64)	0.20 (0.57)	-0.97 (0.59)	-0.07 (0.59)	0.29 (0.50)	—		
9	-0.11 (0.36)	-0.42 (0.39)	-0.65 (0.62)	0.27 (0.55)	-0.91 (0.58)	-0.01 (0.57)	0.35 (0.48)	0.06 (0.54)	—	
10	-0.29 (0.15)	-0.61* (0.19)	-0.84 (0.52)	0.08 (0.43)	-1.09* (0.47)	-0.19 (0.41)	0.17 (0.33)	-0.12 (0.42)	-0.19 (0.40)	—
11	-0.20 (0.44)	-0.52 (0.46)	-0.74 (0.67)	0.17 (0.60)	-1.00* (0.44)	-0.10 (0.62)	0.26 (0.53)	-0.03 (0.58)	-0.09 (0.57)	0.09 (0.46)
12	-0.16 (0.22)	-0.48 (0.26)	-0.70 (0.55)	0.21 (0.47)	-0.96* (0.50)	-0.06 (0.49)	0.30 (0.38)	0.01 (0.46)	-0.05 (0.43)	0.14 (0.26)
13	-0.92 (0.49)	-1.24* (0.49)	-1.47* (0.69)	-0.55 (0.27)	-1.72* (0.66)	-0.82 (0.65)	-0.46 (0.56)	-0.75 (0.63)	-0.82 (0.61)	-0.63 (0.51)
14	-1.53* (0.73)	-1.85* (0.73)	-2.07* (0.88)	-1.16 (0.61)	-2.33* (0.86)	-1.43 (0.85)	-1.07 (0.79)	-1.36 (0.83)	-1.42 (0.82)	-1.24 (0.75)
15	-1.99* (0.83)	-2.31* (0.83)	-2.53* (0.97)	-1.62* (0.73)	-2.79* (0.94)	-1.89* (0.93)	-1.53 (0.88)	-1.82* (0.92)	-1.89* (0.91)	-1.70* (0.84)
16	0.35 (0.31)	0.03 (0.27)	-0.20 (0.40)	0.72 (0.49)	-0.45 (0.54)	0.45 (0.53)	0.81* (0.39)	0.52 (0.50)	0.45 (0.47)	0.64 (0.33)
17	0.01 (0.25)	-0.31 (0.29)	-0.53 (0.57)	0.38 (0.48)	-0.79 (0.51)	0.11 (0.51)	0.47 (0.40)	0.18 (0.47)	0.12 (0.44)	0.31 (0.29)
18	-0.02 (0.23)	-0.34 (0.27)	-0.56 (0.56)	0.35 (0.47)	-0.82 (0.50)	0.08 (0.50)	0.44 (0.38)	0.15 (0.46)	0.09 (0.43)	0.28 (0.28)
19	0.22 (0.34)	-0.10 (0.31)	-0.32 (0.58)	0.59 (0.51)	-0.58 (0.56)	0.32 (0.55)	0.68 (0.42)	0.39 (0.52)	0.33 (0.50)	0.51 (0.36)
Treatment	11	12	13	14	15	16	17	18	19	
11	—									
12	0.04	—								

	(0.50)									
13	-0.72 (0.66)	-0.77 (0.54)	—							
14	-1.33 (0.86)	-1.37 (0.76)	-0.61 (0.55)	—						
15	-1.79 (0.94)	-1.84* (0.86)	-1.07 (0.68)	-0.46 (0.40)	—					
16	0.55 (0.54)	0.50 (0.38)	1.27* (0.56)	1.88* (0.79)	2.34* (0.88)	—				
17	0.21 (0.51)	0.17 (0.34)	0.94 (0.55)	1.54* (0.78)	2.01* (0.87)	-0.33 (0.39)	—			
18	0.18 (0.49)	0.14 (0.32)	0.90 (0.54)	1.51 (0.77)	1.97* (0.86)	-0.37 (0.38)	-0.03 (0.34)	—		
19	0.42 (0.56)	0.38 (0.40)	1.14 (0.58)	1.75* (0.80)	2.21* (0.88)	-0.13 (0.41)	0.21 (0.42)	0.24 (0.41)	—	

* Statistically significant

**Legend:

- | | | |
|---------------------------------|---|---|
| 1. SRP | 8. SRP + powered subgingival water irrigation | 15. SRP + Doxy + aPDT + intensive maintenance |
| 2. Control/no treatment | 9. SRP + SDD | 16. SRP + CHX rinse |
| 3. Intensive OHI | 10. SRP + Doxy | 17. SRP + SMV gel |
| 4. Supragingival cleaning | 11. SRP + AZM | 18. SRP + TET (topical) |
| 5. Supragingival cleaning + AZM | 12. SRP + aPDT | 19. SRP + TET (topical) + intensive maintenance |
| 6. Doxy | 13. SRP + intensive maintenance | |
| 7. OHI + SRP | 14. SRP + Doxy + intensive maintenance | |

INFLUENCE OF LONG TERM USE OF CHX RINSE

Five trials evaluated the effect of mechanical debridement plus/minus CHX rinse. Usually, the use of CHX rinse was no longer than 2 weeks; however, 2 trials prescribed it for over 2 months (Llambés 2012 /2008 / 2005 for 3 months and Santos 2013 for 2 months). In order to explore the influence of long-term use of CHX rinse, we excluded the 2 studies leaving the evidence network with 31 studies, 24 treatments and 2563 participants. There was no evidence of inconsistency in the network (Figure A8.4).

The results were congruent with the primary analysis. SRP still showed a significant effect of reducing HbA1c level as compared to control/no treatment (mean difference was -0.34%; 95% CI: -0.66% to -0.04%). “SRP plus systemic doxycycline, aPDT and intensive maintenance” was still better than SRP monotherapy (mean difference was -2.01%; 95% CI: -3.84% to -0.19%). (Table 3.10)

TABLE 3.10 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITHOUT LONG TERM USE OF CHX RINSE AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.34* (0.16)	—								
3	0.25 (0.53)	-0.09 (0.51)	—							
4	0.23 (0.34)	-0.11 (0.30)	-0.02 (0.54)	—						
5	-0.38 (0.45)	-0.72 (0.45)	-0.63 (0.68)	-0.60 (0.54)	—					
6	0.80 (0.49)	0.46 (0.51)	0.55 (0.72)	0.58 (0.60)	1.18 (0.66)	—				
7	-0.02 (0.49)	-0.36 (0.51)	-0.27 (0.72)	-0.25 (0.59)	0.35 (0.66)	-0.83 (0.69)	—			
8	-0.44 (0.37)	-0.78* (0.34)	-0.69 (0.61)	-0.67 (0.45)	-0.06 (0.56)	-1.24* (0.61)	-0.42 (0.61)	—		
9	-0.16 (0.44)	-0.50 (0.46)	-0.41 (0.69)	-0.39 (0.55)	0.22 (0.63)	-0.96 (0.66)	-0.14 (0.65)	0.28 (0.58)	—	
10	-0.13 (0.25)	-0.47 (0.30)	-0.38 (0.59)	-0.35 (0.42)	0.25 (0.52)	-0.93 (0.55)	-0.10 (0.54)	0.31 (0.45)	0.03 (0.50)	—
11	-0.21 (0.17)	-0.55* (0.21)	-0.46 (0.55)	-0.44 (0.37)	0.16 (0.48)	-1.02 (0.52)	-0.19 (0.46)	0.23 (0.40)	-0.05 (0.47)	-0.09 (0.29)
12	-0.20 (0.47)	-0.54 (0.50)	-0.45 (0.71)	-0.42 (0.58)	0.18 (0.65)	-1.00* (0.48)	-0.17 (0.68)	0.24 (0.60)	-0.04 (0.65)	-0.07 (0.54)
13	0.13 (0.44)	-0.21 (0.46)	-0.12 (0.69)	-0.10 (0.55)	0.50 (0.63)	-0.68 (0.66)	0.15 (0.65)	0.57 (0.57)	0.28 (0.62)	0.25 (0.50)
14	0.28 (0.33)	-0.06 (0.36)	0.03 (0.62)	0.05 (0.47)	0.66 (0.55)	-0.52 (0.59)	0.30 (0.58)	0.72 (0.49)	0.44 (0.55)	0.40 (0.41)
15	-0.14 (0.28)	-0.48 (0.32)	-0.39 (0.60)	-0.36 (0.43)	0.24 (0.52)	-0.94 (0.56)	-0.12 (0.55)	0.30 (0.46)	0.02 (0.52)	-0.01 (0.37)
16	-0.93 (0.56)	-1.27* (0.56)	-1.18 (0.75)	-1.16 (0.63)	-0.56 (0.33)	-1.74* (0.74)	-0.91 (0.74)	-0.49 (0.65)	-0.77 (0.71)	-0.81 (0.61)
17	-1.55 (0.80)	-1.89* (0.80)	-1.80 (0.95)	-1.77* (0.86)	-1.17 (0.67)	-2.35* (0.93)	-1.53 (0.93)	-1.11 (0.87)	-1.39 (0.91)	-1.42 (0.84)
18	-0.03 (0.83)	-0.37 (0.84)	-0.28 (0.97)	-0.26 (0.89)	0.34 (0.71)	-0.84 (0.96)	-0.01 (0.96)	0.41 (0.90)	0.12 (0.94)	0.09 (0.87)
19	-2.01* (0.92)	-2.35* (0.92)	-2.26* (1.05)	-2.24* (0.97)	-1.63* (0.80)	-2.81* (1.03)	-1.99 (1.04)	-1.57 (0.98)	-1.85 (1.02)	-1.89 (0.95)
20	-0.02 (0.35)	-0.36 (0.32)	-0.27 (0.60)	-0.25 (0.43)	0.36 (0.55)	-0.82 (0.60)	0.00 (0.60)	0.42 (0.46)	0.14 (0.56)	0.11 (0.43)
21	0.05 (0.28)	-0.29 (0.23)	-0.20 (0.45)	-0.18 (0.30)	0.43 (0.51)	-0.75 (0.57)	0.07 (0.56)	0.49 (0.41)	0.21 (0.52)	0.17 (0.38)
22	0.01 (0.32)	-0.33 (0.35)	-0.24 (0.62)	-0.22 (0.46)	0.39 (0.55)	-0.79 (0.58)	0.03 (0.58)	0.45 (0.49)	0.17 (0.54)	0.13 (0.40)
23	-0.02 (0.28)	-0.36 (0.32)	-0.27 (0.60)	-0.25 (0.44)	0.36 (0.53)	-0.82 (0.57)	0.00 (0.56)	0.42 (0.47)	0.14 (0.52)	0.11 (0.38)
24	0.24 (0.40)	-0.10 (0.37)	-0.01 (0.63)	0.01 (0.47)	0.61 (0.58)	-0.57 (0.63)	0.26 (0.63)	0.68 (0.50)	0.40 (0.59)	0.36 (0.47)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.02 (0.50)	—								
13	0.34 (0.47)	0.32 (0.64)	—							
14	0.49 (0.37)	0.48 (0.57)	0.15 (0.55)	—						
15	0.07 (0.31)	0.06 (0.55)	-0.26 (0.52)	-0.42 (0.43)	—					
16	-0.72 (0.40)	-0.74 (0.37)	-1.06 (0.63)	-1.21 (0.47)	-0.80 (0.58)	—				

	(0.58)	(0.72)	(0.71)	(0.65)	(0.62)					
17	-1.34 (0.82)	-1.35 (0.92)	-1.67 (0.91)	-1.83* (0.87)	-1.41 (0.85)	-0.61 (0.58)	—			
18	0.18 (0.85)	0.16 (0.95)	-0.16 (0.94)	-0.31 (0.90)	0.10 (0.88)	0.90 (0.62)	1.51 (0.85)	—		
19	-1.80 (0.93)	-1.81 (1.02)	-2.14* (1.02)	-2.29* (0.97)	-1.87 (0.96)	-1.08 (0.73)	-0.46 (0.45)	-1.98* (0.96)	—	
20	0.19 (0.38)	0.18 (0.59)	-0.15 (0.56)	-0.30 (0.48)	0.12 (0.45)	0.91 (0.64)	1.53 (0.86)	0.01 (0.89)	1.99* (0.97)	—
21	0.26 (0.32)	0.25 (0.55)	-0.08 (0.52)	-0.23 (0.43)	0.19 (0.39)	0.98 (0.60)	1.60 (0.84)	0.08 (0.87)	2.06* (0.95)	0.07 (0.39)
22	0.22 (0.36)	0.21 (0.57)	-0.12 (0.54)	-0.27 (0.46)	0.15 (0.42)	0.94 (0.64)	1.56 (0.86)	0.04 (0.89)	2.02* (0.97)	0.03 (0.47)
23	0.19 (0.33)	0.18 (0.55)	-0.15 (0.52)	-0.30 (0.43)	0.12 (0.39)	0.91 (0.62)	1.53 (0.85)	0.01 (0.88)	1.99* (0.96)	0.00 (0.45)
24	0.45 (0.43)	0.43 (0.59)	0.11 (0.52)	-0.04 (0.48)	0.37 (0.48)	1.17 (0.67)	1.78* (0.88)	0.27 (0.91)	2.25* (0.99)	0.26 (0.48)
Treatment	21	22	23	24						
21	—									
22	-0.04 (0.42)	—								
23	-0.07 (0.40)	-0.03 (0.42)	—							
24	0.19 (0.44)	0.23 (0.51)	0.26 (0.49)	—						

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 13. SRP + MTZ + AMX |
| 2. Control/no treatment | 14. SRP + Omega 3 + aspirin |
| 3. Intensive OHI | 15. SRP + aPDT |
| 4. CHX rinse | 16. SRP + intensive maintenance |
| 5. Supragingival cleaning | 17. SRP + Doxy+ intensive maintenance |
| 6. Supragingival cleaning + AZM | 18. SRP + AMX+ intensive maintenance |
| 7. Doxy | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 8. OHI+ SRP | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 9. SRP + powered subgingival water irrigation | 21. SRP + CHX rinse |
| 10. SRP + SDD | 22. SRP + SMV gel |
| 11. SRP + Doxy | 23. SRP + TET (topical) |
| 12. SRP + AZM | 24. SRP + TET (topical) + intensive maintenance |

INFLUENCE OF FM-SRP

As mentioned previously, SRP could be performed either within a short period of time or last for weeks. In order to remove the effect of rapidly finished SRP, this network meta-analysis only included SRP that was performed in the most common way (PM-SRP). This leaves the network meta-analysis with 22 studies, 18 treatments and 2106 patients. There was no evidence of inconsistency in the network (Figure A8.5).

The result showed no significant differences between any of the periodontal treatments and control/no treatment (Table 3.11). Even the effect of SRP on HbA1c was no longer significant. The treatment that had shown significantly lower HbA1c compared with SRP was not contained in this network.

TABLE 3.11 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.36 (0.21)	—								
3	0.25 (0.45)	-0.11 (0.39)	—							
4	-0.35 (0.52)	-0.71 (0.52)	-0.60 (0.65)	—						
5	0.00 (0.57)	-0.36 (0.60)	-0.25 (0.72)	0.35 (0.77)	—					
6	-0.42 (0.48)	-0.78 (0.44)	-0.67 (0.59)	-0.07 (0.67)	-0.43 (0.74)	—				
7	-0.18 (0.37)	-0.54 (0.43)	-0.43 (0.58)	0.17 (0.63)	-0.18 (0.66)	0.24 (0.60)	—			
8	-0.19 (0.21)	-0.55 (0.28)	-0.44 (0.48)	0.16 (0.55)	-0.19 (0.53)	0.23 (0.51)	-0.01 (0.41)	—		
9	0.12 (0.52)	-0.24 (0.56)	-0.13 (0.68)	0.47 (0.73)	0.12 (0.77)	0.54 (0.71)	0.30 (0.63)	0.31 (0.56)	—	
10	0.28 (0.43)	-0.08 (0.47)	0.03 (0.62)	0.63 (0.67)	0.28 (0.71)	0.71 (0.64)	0.46 (0.57)	0.47 (0.47)	0.16 (0.67)	—
11	0.06 (0.63)	-0.30 (0.66)	-0.19 (0.77)	0.41 (0.81)	0.06 (0.83)	0.48 (0.79)	0.24 (0.73)	0.25 (0.63)	-0.06 (0.81)	-0.22 (0.76)
12	-0.90 (0.67)	-1.26 (0.67)	-1.15 (0.78)	-0.55 (0.43)	-0.90 (0.88)	-0.47 (0.80)	-0.72 (0.76)	-0.71 (0.70)	-1.02 (0.85)	-1.18 (0.80)
13	0.00 (0.47)	-0.36 (0.42)	-0.25 (0.57)	0.35 (0.67)	0.00 (0.73)	0.43 (0.60)	0.18 (0.60)	0.19 (0.50)	-0.12 (0.70)	-0.28 (0.63)
14	0.07 (0.37)	-0.29 (0.30)	-0.18 (0.39)	0.42 (0.60)	0.07 (0.67)	0.49 (0.53)	0.25 (0.53)	0.26 (0.41)	-0.05 (0.64)	-0.21 (0.56)
15	0.01 (0.42)	-0.35 (0.47)	-0.24 (0.61)	0.36 (0.66)	0.01 (0.71)	0.43 (0.64)	0.19 (0.56)	0.20 (0.47)	-0.11 (0.66)	-0.27 (0.60)
16	-0.01 (0.43)	-0.37 (0.48)	-0.26 (0.62)	0.34 (0.67)	-0.01 (0.71)	0.41 (0.65)	0.17 (0.57)	0.18 (0.48)	-0.13 (0.67)	-0.29 (0.60)
17	0.26 (0.50)	-0.10 (0.46)	0.02 (0.60)	0.61 (0.69)	0.26 (0.75)	0.69 (0.63)	0.44 (0.63)	0.46 (0.53)	0.14 (0.72)	-0.02 (0.66)
18	0.20 (0.57)	-0.16 (0.54)	-0.05 (0.59)	0.55 (0.74)	0.20 (0.80)	0.63 (0.69)	0.38 (0.68)	0.39 (0.60)	0.08 (0.77)	-0.08 (0.71)
Treatment	11	12	13	14	15	16	17	18		
11	—									
12	-0.96 (0.92)	—								
13	-0.06 (0.78)	0.90 (0.79)	—							
14	0.01 (0.73)	0.97 (0.74)	0.07 (0.52)	—						
15	-0.05 (0.76)	0.91 (0.79)	0.01 (0.63)	-0.06 (0.56)	—					
16	-0.07 (0.76)	0.89 (0.80)	-0.01 (0.64)	-0.08 (0.57)	-0.02 (0.60)	—				
17	0.20 (0.80)	1.16 (0.81)	0.26 (0.62)	0.19 (0.55)	0.25 (0.65)	0.27 (0.66)	—			
18	0.14 (0.85)	1.10 (0.86)	0.20 (0.68)	0.13 (0.44)	0.19 (0.71)	0.21 (0.72)	-0.06 (0.70)	—		

* Statistically significant

**Legend:

- | | | |
|---------------------------|---------------------------------|---|
| 1. SRP | 7. SRP + SDD | 13. SRP/flap surgery+ Tinidazole + Ampicillin |
| 2. Control/no treatment | 8. SRP + Doxy | 14. SRP + CHX rinse |
| 3. CHX rinse | 9. SRP + MTZ + AMX | 15. SRP + SMV gel |
| 4. Supragingival cleaning | 10. SRP + Omega 3 + aspirin | 16. SRP + TET (topical) |
| 5. Doxy | 11. SRP + aPDT | 17. SRP + TET (topical) + intensive maintenance |
| 6. OHI+ SRP | 12. SRP + intensive maintenance | 18. SRP + CHX rinse + Doxy |

End of study

The evidence network for HbA1c using the end of study results included 35 studies, 2711 participants and 30 treatments, providing 54 comparisons based on 27 trials with 2 arms, 7 trials with 3 arms and 1 trial with 4 arms. Three trials reporting HbA1c were excluded from this network meta-analysis for one of the 2 reasons: comparison of FMSRP with PMSRP (Santos 2012; Santos 2009) or treatments were not connected to the network (Khader 2010). There was no evidence of inconsistency in the network (Figure A8.9).

By the end of study, SPR showed a significant effect, reducing blood HbA1c level as compared to control/no treatment (mean difference was -0.38%; 95% CI: -0.70% to -0.08%). There was no difference between other periodontal therapies and SRP (Table 3.12-3.13). It is noteworthy that the treatment that was shown to be significantly different from SRP at 3 months, in terms of reducing HbA1c, was no longer statistically significant when the time was changed to end of study.

The estimates from the fix-effects model were consistent with the estimates from the primary trials (direct evidence) (Figure 3.4), in which “SRP plus systemic doxycycline” and “SRP plus aPDT” were significantly better than SRP. However, the significant effect was not found in the random-effects model. Based on DIC and total residual deviance, the random-effects model was considered to be a better fit (Table 3.14).

TABLE 3.12 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.38* (0.16)	—								
3	-0.01 (0.54)	-0.39 (0.52)	—							
4	0.12 (0.33)	-0.26 (0.29)	0.13 (0.52)	—						
5	0.29 (0.28)	-0.09 (0.29)	0.30 (0.59)	0.17 (0.41)	—					
6	0.10 (0.46)	-0.28 (0.48)	0.11 (0.71)	-0.02 (0.56)	-0.19 (0.54)	—				
7	-0.02 (0.46)	-0.39 (0.47)	0.00 (0.70)	-0.14 (0.55)	-0.31 (0.54)	-0.12 (0.65)	—			
8	-0.17 (0.42)	-0.54 (0.44)	-0.15 (0.68)	-0.28 (0.53)	-0.45 (0.51)	-0.26 (0.62)	-0.15 (0.62)	—		
9	-0.14	-0.51	-0.12	-0.26	-0.43	-0.23	-0.12	0.03	—	

	(0.26)	(0.29)	(0.60)	(0.41)	(0.37)	(0.52)	(0.52)	(0.49)		
10	-0.21 (0.16)	-0.59* (0.20)	-0.20 (0.56)	-0.33 (0.35)	-0.50 (0.31)	-0.31 (0.48)	-0.19 (0.43)	-0.05 (0.45)	-0.07 (0.29)	—
11	-0.60 (0.48)	-0.97 (0.50)	-0.58 (0.73)	-0.72 (0.57)	-0.89 (0.55)	-0.70 (0.45)	-0.58 (0.66)	-0.43 (0.63)	-0.46 (0.54)	-0.39 (0.50)
12	-0.19 (0.77)	-0.57 (0.78)	-0.18 (0.94)	-0.31 (0.83)	-0.48 (0.81)	-0.29 (0.89)	-0.17 (0.88)	-0.03 (0.87)	-0.05 (0.81)	0.02 (0.78)
13	-0.02 (0.29)	-0.40 (0.33)	-0.01 (0.62)	-0.14 (0.44)	-0.31 (0.40)	-0.12 (0.54)	0.00 (0.54)	0.14 (0.51)	0.12 (0.39)	0.19 (0.33)
14	-0.14 (0.25)	-0.52 (0.29)	-0.13 (0.59)	-0.26 (0.41)	-0.43 (0.37)	-0.24 (0.52)	-0.13 (0.52)	0.02 (0.49)	-0.01 (0.36)	0.07 (0.28)
15	-0.23 (0.25)	-0.60* (0.25)	-0.21 (0.58)	-0.35 (0.38)	-0.52* (0.27)	-0.32 (0.52)	-0.21 (0.52)	-0.06 (0.49)	-0.09 (0.33)	-0.02 (0.29)
16	-0.31 (0.34)	-0.68* (0.33)	-0.29 (0.61)	-0.43 (0.43)	-0.60 (0.39)	-0.41 (0.57)	-0.29 (0.57)	-0.14 (0.54)	-0.17 (0.41)	-0.10 (0.37)
17	-0.68 (0.35)	-1.06* (0.32)	-0.67 (0.61)	-0.80 (0.43)	-0.97* (0.43)	-0.78 (0.58)	-0.67 (0.57)	-0.52 (0.55)	-0.55 (0.43)	-0.47 (0.37)
18	0.21 (0.39)	-0.16 (0.41)	0.23 (0.66)	0.09 (0.50)	-0.08 (0.46)	0.12 (0.60)	0.23 (0.60)	0.38 (0.57)	0.35 (0.40)	0.42 (0.42)
19	-0.80 (0.61)	-1.18 (0.61)	-0.79 (0.80)	-0.92 (0.67)	-1.09 (0.62)	-0.90 (0.77)	-0.78 (0.76)	-0.64 (0.74)	-0.66 (0.64)	-0.59 (0.62)
20	0.65 (0.65)	0.28 (0.65)	0.67 (0.83)	0.53 (0.71)	0.36 (0.66)	0.56 (0.80)	0.67 (0.80)	0.82 (0.78)	0.79 (0.69)	0.86 (0.67)
21	0.61 (0.57)	0.23 (0.56)	0.62 (0.76)	0.49 (0.63)	0.32 (0.57)	0.51 (0.73)	0.62 (0.73)	0.77 (0.70)	0.74 (0.60)	0.82 (0.58)
22	-1.26 (0.74)	-1.63* (0.74)	-1.24 (0.90)	-1.38 (0.79)	-1.55* (0.74)	-1.36 (0.87)	-1.24 (0.87)	-1.09 (0.85)	-1.12 (0.77)	-1.05 (0.75)
23	0.02 (0.32)	-0.36 (0.28)	0.03 (0.59)	-0.10 (0.40)	-0.27 (0.40)	-0.08 (0.56)	0.03 (0.55)	0.18 (0.53)	0.15 (0.41)	0.23 (0.34)
24	-0.21 (0.33)	-0.58 (0.29)	-0.19 (0.43)	-0.33 (0.29)	-0.50 (0.41)	-0.31 (0.56)	-0.19 (0.55)	-0.04 (0.53)	-0.07 (0.41)	0.00 (0.35)
25	0.02 (0.28)	-0.36 (0.32)	0.03 (0.61)	-0.10 (0.43)	-0.27 (0.40)	-0.08 (0.54)	0.04 (0.54)	0.19 (0.50)	0.16 (0.38)	0.23 (0.32)
26	-0.01 (0.29)	-0.38 (0.33)	0.01 (0.62)	-0.13 (0.44)	-0.30 (0.41)	-0.10 (0.54)	0.01 (0.54)	0.16 (0.51)	0.13 (0.39)	0.20 (0.33)
27	0.17 (0.36)	-0.20 (0.33)	0.19 (0.61)	0.05 (0.44)	-0.12 (0.44)	0.07 (0.58)	0.19 (0.57)	0.34 (0.55)	0.31 (0.44)	0.38 (0.38)
28	0.05 (0.65)	-0.32 (0.64)	0.07 (0.82)	-0.06 (0.70)	-0.23 (0.67)	-0.04 (0.79)	0.07 (0.78)	0.22 (0.77)	0.19 (0.69)	0.27 (0.66)
29	0.46 (0.33)	0.08 (0.29)	0.47 (0.59)	0.34 (0.41)	0.17 (0.41)	0.36 (0.56)	0.48 (0.56)	0.62 (0.53)	0.60 (0.41)	0.67 (0.35)
30	-0.08 (0.45)	-0.46 (0.42)	-0.07 (0.53)	-0.20 (0.42)	-0.37 (0.51)	-0.18 (0.64)	-0.06 (0.64)	0.09 (0.62)	0.06 (0.52)	0.13 (0.47)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.41 (0.90)	—								
13	0.58 (0.56)	0.17 (0.82)	—							
14	0.45 (0.53)	0.05 (0.81)	-0.12 (0.38)	—						
15	0.37 (0.54)	-0.03 (0.81)	-0.21 (0.38)	-0.08 (0.36)	—					
16	0.29 (0.58)	-0.12 (0.84)	-0.29 (0.45)	-0.16 (0.42)	-0.08 (0.32)	—				
17	-0.09 (0.59)	-0.49 (0.85)	-0.66 (0.46)	-0.54 (0.43)	-0.46 (0.40)	-0.38 (0.46)	—			
18	0.81 (0.62)	0.41 (0.86)	0.23 (0.49)	0.36 (0.46)	0.44 (0.42)	0.52 (0.50)	0.90 (0.52)	—		
19	-0.20 (0.78)	-0.61 (0.98)	-0.78 (0.67)	-0.66 (0.66)	-0.57 (0.56)	-0.49 (0.64)	-0.12 (0.69)	-1.01 (0.69)	—	
20	1.25 (0.81)	0.84 (1.03)	0.67 (0.71)	0.80 (0.70)	0.88 (0.61)	0.96 (0.68)	1.34 (0.72)	0.44 (0.73)	1.45 (0.82)	—

21	1.20 (0.74)	0.80 (0.95)	0.63 (0.64)	0.75 (0.62)	0.83 (0.50)	0.91 (0.59)	1.29 (0.65)	0.39 (0.65)	1.41 (0.75)	-0.05 (0.79)
22	-0.66 (0.88)	-1.07 (1.07)	-1.24 (0.79)	-1.11 (0.78)	-1.03 (0.69)	-0.95 (0.76)	-0.57 (0.80)	-1.47 (0.81)	-0.46 (0.42)	-1.91* (0.91)
23	0.61 (0.58)	0.21 (0.83)	0.04 (0.43)	0.16 (0.40)	0.24 (0.38)	0.32 (0.43)	0.70 (0.43)	-0.20 (0.50)	0.82 (0.67)	-0.64 (0.71)
24	0.39 (0.58)	-0.02 (0.83)	-0.19 (0.44)	-0.06 (0.41)	0.02 (0.38)	0.10 (0.44)	0.48 (0.43)	-0.42 (0.51)	0.59 (0.67)	-0.86 (0.71)
25	0.62 (0.55)	0.21 (0.82)	0.04 (0.40)	0.16 (0.37)	0.25 (0.38)	0.33 (0.44)	0.70 (0.45)	-0.19 (0.48)	0.82 (0.67)	-0.63 (0.71)
26	0.59 (0.56)	0.18 (0.82)	0.01 (0.41)	0.14 (0.39)	0.22 (0.39)	0.30 (0.45)	0.68 (0.46)	-0.22 (0.49)	0.79 (0.68)	-0.66 (0.72)
27	0.77 (0.60)	0.36 (0.85)	0.19 (0.46)	0.32 (0.44)	0.40 (0.41)	0.48 (0.46)	0.86 (0.46)	-0.04 (0.53)	0.97 (0.69)	-0.48 (0.73)
28	0.65 (0.80)	0.25 (1.00)	0.08 (0.71)	0.20 (0.70)	0.28 (0.64)	0.36 (0.56)	0.74 (0.71)	-0.16 (0.74)	0.86 (0.85)	-0.60 (0.89)
29	1.06 (0.58)	0.65 (0.84)	0.48 (0.44)	0.60 (0.41)	0.68 (0.38)	0.77 (0.43)	1.14* (0.43)	0.24 (0.50)	1.26 (0.67)	-0.19 (0.71)
30	0.52 (0.65)	0.11 (0.89)	-0.06 (0.54)	0.06 (0.52)	0.15 (0.49)	0.23 (0.53)	0.60 (0.53)	-0.29 (0.59)	0.72 (0.74)	-0.73 (0.77)
Treatment	21	22	23	24	25	26	27	28	29	30
21	—									
22	-1.86* (0.86)	—								
23	-0.59 (0.63)	1.27 (0.79)	—							
24	-0.81 (0.63)	1.05 (0.79)	-0.22 (0.40)	—						
25	-0.59 (0.63)	1.28 (0.79)	0.00 (0.43)	0.23 (0.43)	—					
26	-0.61 (0.64)	1.25 (0.79)	-0.02 (0.44)	0.20 (0.44)	-0.03 (0.41)	—				
27	-0.43 (0.65)	1.43 (0.80)	0.16 (0.43)	0.38 (0.44)	0.15 (0.46)	0.18 (0.47)	—			
28	-0.55 (0.81)	1.31 (0.94)	0.04 (0.70)	0.26 (0.70)	0.03 (0.70)	0.06 (0.71)	-0.12 (0.72)	—		
29	-0.15 (0.63)	1.72* (0.79)	0.44 (0.41)	0.67 (0.41)	0.44 (0.43)	0.47 (0.44)	0.29 (0.44)	0.40 (0.70)	—	
30	-0.69 (0.70)	1.18 (0.85)	-0.10 (0.51)	0.13 (0.31)	-0.10 (0.53)	-0.07 (0.54)	-0.25 (0.54)	-0.14 (0.77)	-0.54 (0.52)	—

* Statistically significant;

**Legend:

- | | | |
|---|--|---|
| 1. SRP | 11. SRP + AZM | 21. SRP + MTZ + AMX + intensive maintenance |
| 2. Control/no treatment | 12. SRP + ALN | 22. SRP + Doxy + aPDT + intensive maintenance |
| 3. Intensive OHI | 13. SRP + Omega 3 + aspirin | 23. SRP/flap surgery+ Tinidazole + Ampicillin |
| 4. CHX rinse | 14. SRP + aPDT | 24. SRP + CHX rinse |
| 5. Supragingival cleaning | 15. SRP + intensive maintenance | 25. SRP + SMV gel |
| 6. Supragingival cleaning + AZM | 16. SRP + non-intensive maintenance | 26. SRP + TET (topical) |
| 7. Doxy | 17. OHI + SRP + intensive maintenance | 27. SRP + TET (topical) + intensive maintenance |
| 8. SRP + powered subgingival water irrigation | 18. SRP + SDD + intensive maintenance | 28. SRP + TET (topical) + non-intensive maintenance |
| 9. SRP + SDD | 19. SRP + Doxy + intensive maintenance | 29. SRP + CHX rinse + intensive maintenance |
| 10. SRP + Doxy | 20. SRP + AMX + intensive maintenance | 30. SRP + CHX rinse + Doxy |

**TABLE 3.13 HbA1c ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

T**	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	26	27	28	29	30
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T: treatment

**Legend: same as table 3.11

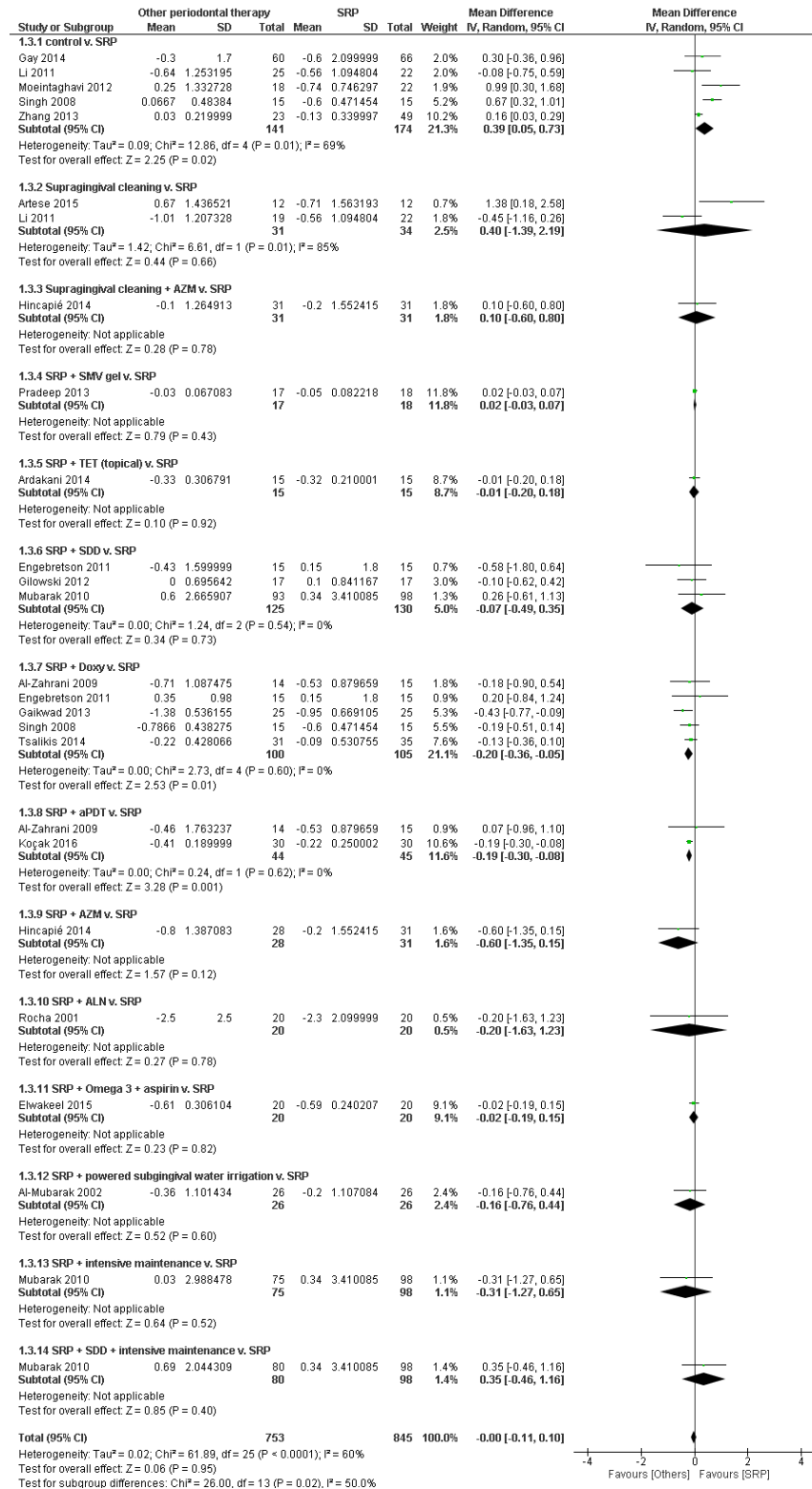
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.14 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR HBA1C AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	0.39* (0.05 to 0.73)	5	69%	0.38* (0.08 to 0.70)	0.25* (0.13 to 0.36)
Supragingival cleaning	SRP	0.40 (-1.39 to 2.19)	2	85%	0.29 (-0.26 to 0.85)	0.24 (-0.13 to 0.63)
Supragingival cleaning + AZM	SRP	0.10 (-0.60 to 0.80)	1	NA	0.10 (-0.80 to 0.99)	0.11 (-0.59 to 0.82)
SRP + SMV gel	SRP	0.02 (-0.03 to 0.07)	1	NA	0.02 (-0.56 to 0.61)	0.02 (-0.03 to 0.07)
SRP + TET (topical)	SRP	-0.01 (-0.20 to 0.18)	1	NA	-0.01 (-0.61 to 0.59)	-0.01 (-0.20 to 0.18)
SRP + SDD	SRP	-0.07 (-0.49 to 0.35)	3	0%	-0.14 (-0.65 to 0.38)	-0.14 (-0.52 to 0.25)
SRP + Doxy	SRP	-0.20* (-0.36 to -0.05)	5	0%	-0.21 (-0.51 to 0.12)	-0.25* (-0.40 to -0.10)
SRP + aPDT	SRP	-0.19* (-0.30 to -0.08)	2	0%	-0.14 (-0.63 to 0.39)	-0.19* (-0.30 to -0.07)
SRP + AZM	SRP	-0.60 (-1.35 to 0.15)	1	NA	-0.60 (-1.54 to 0.34)	-0.59 (-1.34 to 0.16)
SRP + ALN	SRP	-0.20 (-1.63 to 1.23)	1	NA	-0.19 (-1.73 to 1.30)	-0.20 (-1.63 to 1.23)
SRP + Omega 3 + aspirin	SRP	-0.02 (-0.19 to 0.15)	1	NA	-0.02 (-0.62 to 0.57)	-0.02 (-0.19 to 0.15)
SRP + powered subgingival water irrigation	SRP	-0.16 (-0.76 to 0.44)	1	NA	-0.17 (-0.98 to 0.67)	-0.16 (-0.75 to 0.45)
SRP + intensive maintenance	SRP	-0.31 (-1.27 to 0.65)	1	NA	-0.23 (-0.74 to 0.27)	-0.27 (-0.59 to 0.04)
SRP + SDD + intensive maintenance	SRP	0.35 (-0.46 to 1.16)	1	NA	0.21 (-0.57 to 0.99)	0.19 (-0.42 to 0.79)
				DIC	1.213	6.421
				Total residual deviance (Unconstrained data points)	80.53 (79 points)	92.33 (79 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.4 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON HBA1C AT END OF STUDY



SENSITIVITY ANALYSIS

INFLUENCE OF FUNDING

The network involving trials with no industry funding by end of study included 22 studies, 2021 patients and 17 treatments. There was no evidence of inconsistency in the network (Figure A8.10).

The results are congruent with the primary analysis (Table 3.15). Compared to the control/no treatment group, SRP was shown to significantly reduce the level of HbA1c (mean difference was -0.40%; 95% CI: -0.79% to -0.06%). There was no statistical difference between other periodontal therapies and SRP.

TABLE 3.15 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH NO INDUSTRY FUNDING AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.40* (0.18)	—								
3	0.30 (0.32)	-0.10 (0.32)	—							
4	-0.13 (0.29)	-0.53 (0.33)	-0.43 (0.41)	—						
5	-0.14 (0.25)	-0.54 (0.28)	-0.44 (0.39)	-0.01 (0.36)	—					
6	-0.19 (0.81)	-0.59 (0.83)	-0.49 (0.87)	-0.06 (0.86)	-0.05 (0.85)	—				
7	-0.02 (0.37)	-0.42 (0.41)	-0.32 (0.48)	0.11 (0.47)	0.12 (0.44)	0.17 (0.89)	—			
8	-0.12 (0.30)	-0.52 (0.35)	-0.42 (0.43)	0.01 (0.42)	0.02 (0.37)	0.07 (0.87)	-0.10 (0.47)	—		
9	-0.22 (0.29)	-0.62* (0.28)	-0.52 (0.31)	-0.09 (0.37)	-0.08 (0.37)	-0.03 (0.86)	-0.20 (0.47)	-0.10 (0.42)	—	
10	-0.29 (0.41)	-0.69 (0.39)	-0.59 (0.46)	-0.16 (0.48)	-0.15 (0.46)	-0.10 (0.91)	-0.27 (0.55)	-0.17 (0.51)	-0.07 (0.38)	—
11	0.23 (0.44)	-0.17 (0.46)	-0.07 (0.51)	0.36 (0.45)	0.37 (0.50)	0.42 (0.92)	0.25 (0.57)	0.35 (0.53)	0.45 (0.46)	0.52 (0.56)
12	-0.81 (0.67)	-1.21 (0.67)	-1.11 (0.68)	-0.68 (0.71)	-0.67 (0.71)	-0.62 (1.06)	-0.79 (0.77)	-0.69 (0.74)	-0.59 (0.60)	-0.52 (0.71)
13	0.69 (0.71)	0.29 (0.70)	0.39 (0.72)	0.82 (0.75)	0.83 (0.75)	0.88 (1.08)	0.71 (0.80)	0.81 (0.77)	0.91 (0.64)	0.98 (0.75)
14	0.61 (0.63)	0.20 (0.62)	0.31 (0.64)	0.74 (0.67)	0.75 (0.67)	0.80 (1.02)	0.63 (0.73)	0.73 (0.70)	0.83 (0.55)	0.90 (0.67)
15	-1.27 (0.83)	-1.67* (0.82)	-1.57 (0.83)	-1.14 (0.86)	-1.13 (0.86)	-1.08 (1.16)	-1.25 (0.90)	-1.15 (0.88)	-1.05 (0.77)	-0.98 (0.86)
16	0.04 (0.40)	-0.36 (0.36)	-0.26 (0.48)	0.17 (0.49)	0.18 (0.45)	0.23 (0.91)	0.06 (0.54)	0.17 (0.50)	0.26 (0.46)	0.33 (0.53)
17	0.50 (0.40)	0.10 (0.35)	0.20 (0.47)	0.63 (0.48)	0.64 (0.45)	0.69 (0.91)	0.52 (0.54)	0.62 (0.49)	0.72 (0.43)	0.79 (0.51)
Treatment	11	12	13	14	15	16	17			

11	—									
12	-1.04 (0.76)	—								
13	0.46 (0.80)	1.50 (0.88)	—							
14	0.38 (0.72)	1.42 (0.82)	-0.09 (0.86)	—						
15	-1.50 (0.90)	-0.46 (0.48)	-1.96 (1.00)	-1.87* (0.95)	—					
16	-0.19 (0.58)	0.86 (0.76)	-0.65 (0.79)	-0.56 (0.72)	1.31 (0.90)	—				
17	0.27 (0.57)	1.31 (0.74)	-0.19 (0.77)	-0.11 (0.71)	1.77* (0.88)	0.45 (0.50)	—			

* Statistically significant

**Legend:

- | | |
|--------------------------------|---|
| 1. SRP | 10. SRP + non-intensive maintenance |
| 2. Control/no treatment | 11. SRP + SDD + intensive maintenance |
| 3. Supragingival cleaning | 12. SRP + Doxy + intensive maintenance |
| 4. SRP + SDD | 13. SRP + AMX + intensive maintenance |
| 5. SRP + Doxy | 14. SRP + MTZ + AMX + intensive maintenance |
| 6. SRP + ALN | 15. SRP + Doxy + aPDT + intensive maintenance |
| 7. SRP + Omega 3 + aspirin | 16. SRP/flap surgery+ Tinidazole + Ampicillin |
| 8. SRP + aPDT | 17. SRP + CHX rinse + intensive maintenance |
| 9. SRP + intensive maintenance | |

INFLUENCE OF RISK OF BIAS

Nine trials were excluded from this network meta-analysis for being considered at high overall risk of bias (Table 3.16). Raman 2014 was also excluded for not connected in the new network. This left the analysis with 25 trials and 21 treatments involving 1848 patients. There was no evidence of inconsistency in the network (Figure A8.11).

The results were congruent with the primary analysis (Table 3.17). Compared to the control/no treatment group, SRP was shown to significantly reduce the level of HbA1c (mean difference was -0.39%; 95% CI: -0.76% to -0.08%). There was no statistical difference between other periodontal therapies and SRP.

TABLE 3.16: RISK OF BIAS ASSESSMENT OF TRIALS THAT REPORTED HBA1C AT END OF STUDY

Trial	sequence generation	Allocation concealment	Blinding (subjective outcomes)	Incomplete data addressed (efficacy)	Overall judgment
Tsalikis 2014	Low	Unclear	Unclear	Low	Unclear
Miranda 2014	Low	Low	Low	High	High
Raman 2014	Unclear	Unclear	Unclear	Unclear	Unclear
Hincapié 2014	Low	Low	Unclear	Low	Unclear
Macedo 2013	Low	Unclear	Unclear	Low	Unclear
Engebretson 2013	Unclear	Unclear	Unclear	Low	Unclear
Li 2011	Low	Unclear	Unclear	Unclear	Unclear
Chen 2012	Low	Low	Unclear	Low	Unclear
Koromantzios 2011	Low	Unclear	Low	Low	Unclear
Pradeep 2013	Low	Low	Low	Low	Low
Santos 2013	Low	Unclear	High	Low	High
Gilowski 2012	Unclear	Unclear	Low	Unclear	Unclear
Moeintaghavi 2012	Low	Unclear	Unclear	Low	Unclear
Engebretson 2011	Low	Unclear	N/A	High	High
Mubarak 2010	High	High	Unclear	Unclear	High
Al-Zahrani 2009	Low	Unclear	Unclear	Low	Unclear
Katagiri 2008	Unclear	Unclear	Unclear	Low	Unclear
O'Connell 2008	Unclear	Unclear	Unclear	Unclear	Unclear
Llambés 2008	Unclear	High	Unclear	High	High
Skaleric 2004	Unclear	Unclear	Unclear	Low	Unclear
Al-Mubarak 2002	Unclear	Low	Low	Low	Unclear
Rocha 2001	Unclear	Unclear	Unclear	Unclear	Unclear
Kaur 2015	Low	Unclear	Low	Low	Unclear
Rodrigues 2003	Unclear	Unclear	High	Unclear	High
Fu 2006	Unclear	Unclear	Unclear	Low	Unclear
Singh 2008	Unclear	Unclear	Unclear	Low	Unclear
Sun 2011	Unclear	Unclear	High	Unclear	High
Telgi 2013	Unclear	Unclear	High	Low	High
Gay 2014	Low	Unclear	Unclear	Low	Unclear
Artese 2015	Low	Low	Low	Low	Low
Gaikwad 2013	Unclear	Unclear	Unclear	Unclear	Unclear
Elwakeel 2015	Low	Low	Low	High	High
Ardakani 2014	Unclear	Unclear	Unclear	Unclear	Unclear
Zhang 2013	Low	Unclear	Unclear	Low	Unclear
Koçak 2016	Low	Low	N/A	Low	Low

TABLE 3.17 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS AT LOW RISK OF BIAS/UNCLEAR AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.39* (0.17)	—									
3	0.35 (0.31)	-0.04 (0.30)	—								
4	0.10 (0.47)	-0.29 (0.49)	-0.25 (0.56)	—							
5	-0.08 (0.48)	-0.47 (0.51)	-0.43 (0.57)	-0.18 (0.67)	—						
6	-0.16 (0.44)	-0.55 (0.47)	-0.52 (0.53)	-0.26 (0.64)	-0.08 (0.65)	—					
7	-0.10 (0.41)	-0.49 (0.44)	-0.46 (0.51)	-0.20 (0.62)	-0.02 (0.63)	0.06 (0.60)	—				
8	-0.28 (0.18)	-0.67* (0.23)	-0.63 (0.35)	-0.38 (0.50)	-0.20 (0.45)	-0.12 (0.47)	-0.18 (0.44)	—			
9	-0.60 (0.49)	-0.99* (0.52)	-0.96 (0.58)	-0.70 (0.47)	-0.52 (0.69)	-0.44 (0.65)	-0.50 (0.63)	-0.32 (0.52)	—		
10	-0.20 (0.78)	-0.59 (0.80)	-0.55 (0.84)	-0.30 (0.91)	-0.12 (0.92)	-0.04 (0.90)	-0.10 (0.88)	0.08 (0.80)	0.41 (0.92)	—	
11	-0.15 (0.27)	-0.54 (0.31)	-0.50 (0.40)	-0.25 (0.54)	-0.07 (0.55)	0.02 (0.51)	-0.04 (0.49)	0.13 (0.31)	0.46 (0.56)	0.05 (0.82)	—
12	-0.10 (0.33)	-0.49 (0.30)	-0.45 (0.30)	-0.20 (0.56)	-0.02 (0.58)	0.06 (0.54)	0.00 (0.52)	0.18 (0.36)	0.50 (0.59)	0.10 (0.85)	0.05 (0.42)
13	-0.23 (0.39)	-0.62 (0.35)	-0.59 (0.41)	-0.34 (0.61)	-0.15 (0.61)	-0.07 (0.58)	-0.13 (0.56)	0.05 (0.41)	0.37 (0.62)	-0.04 (0.87)	-0.09 (0.47)
14	-0.67 (0.38)	-1.06* (0.34)	-1.02* (0.46)	-0.77 (0.60)	-0.59 (0.61)	-0.51 (0.58)	-0.57 (0.56)	-0.39 (0.41)	-0.06 (0.62)	-0.47 (0.87)	-0.52 (0.46)
15	-0.68 (0.66)	-1.07 (0.65)	-1.04 (0.64)	-0.78 (0.81)	-0.60 (0.82)	-0.52 (0.79)	-0.58 (0.78)	-0.40 (0.68)	-0.08 (0.82)	-0.48 (1.03)	-0.53 (0.71)
16	-1.14 (0.80)	-1.53 (0.79)	-1.49 (0.78)	-1.24 (0.92)	-1.06 (0.93)	-0.97 (0.90)	-1.03 (0.90)	-0.86 (0.81)	-0.53 (0.93)	-0.94 (1.12)	-0.99 (0.84)
17	0.02 (0.31)	-0.37 (0.35)	-0.34 (0.43)	-0.08 (0.56)	0.10 (0.57)	0.18 (0.53)	0.12 (0.51)	0.30 (0.35)	0.62 (0.58)	0.22 (0.84)	0.17 (0.41)
18	-0.01 (0.32)	-0.40 (0.36)	-0.36 (0.44)	-0.11 (0.56)	0.07 (0.58)	0.15 (0.54)	0.09 (0.52)	0.27 (0.37)	0.59 (0.58)	0.19 (0.85)	0.14 (0.41)
19	0.20 (0.39)	-0.19 (0.35)	-0.16 (0.46)	0.09 (0.60)	0.28 (0.61)	0.36 (0.58)	0.30 (0.56)	0.48 (0.42)	0.80 (0.62)	0.39 (0.87)	0.34 (0.47)
20	0.13 (0.70)	-0.26 (0.68)	-0.22 (0.72)	0.03 (0.84)	0.21 (0.85)	0.29 (0.82)	0.23 (0.81)	0.41 (0.72)	0.73 (0.85)	0.33 (1.05)	0.28 (0.75)
21	0.45 (0.37)	0.06 (0.33)	0.10 (0.45)	0.35 (0.60)	0.53 (0.61)	0.61 (0.57)	0.55 (0.55)	0.73 (0.40)	1.05 (0.62)	0.65 (0.87)	0.60 (0.46)
Treatment	12	13	14	15	16	17	18	19	20	21	
12	—										
13	-0.13 (0.35)	—									
14	-0.57 (0.45)	-0.43 (0.49)	—								
15	-0.58 (0.57)	-0.45 (0.67)	-0.01 (0.73)	—							
16	-1.04 (0.73)	-0.90 (0.81)	-0.47 (0.86)	-0.45 (0.44)	—						
17	0.12 (0.45)	0.25 (0.49)	0.69 (0.49)	0.70 (0.73)	1.15 (0.85)	—					
18	0.09 (0.46)	0.22 (0.50)	0.66 (0.50)	0.67 (0.73)	1.13 (0.86)	-0.03 (0.45)	—				
19	0.30 (0.46)	0.43 (0.50)	0.86 (0.49)	0.88 (0.74)	1.33 (0.86)	0.18 (0.50)	0.21 (0.50)	—			
20	0.23	0.36	0.80	0.81	1.27	0.11	0.14	-0.07	—		

	(0.68)	(0.59)	(0.76)	(0.89)	(1.00)	(0.76)	(0.77)	(0.77)			
21	0.55 (0.45)	0.68 (0.49)	1.12* (0.48)	1.13 (0.73)	1.59 (0.85)	0.43 (0.48)	0.46 (0.49)	0.25 (0.49)	0.32 (0.76)	—	

* Statistically significant

**Legend:

- | | | |
|---|---------------------------------------|---|
| 1. SRP | 8. SRP + Doxy | 15. SRP + Doxy + intensive maintenance |
| 2. Control/no treatment | 9. SRP + AZM | 16. SRP + Doxy + aPDT + intensive maintenance |
| 3. Supragingival cleaning | 10. SRP + ALN | 17. SRP + SMV gel |
| 4. Supragingival cleaning + AZM | 11. SRP + aPDT | 18. SRP + TET (topical) |
| 5. Doxy | 12. SRP + intensive maintenance | 19. SRP + TET (topical) + intensive maintenance |
| 6. SRP + powered subgingival water irrigation | 13. SRP + non-intensive maintenance | 20. SRP + TET (topical) + non-intensive maintenance |
| 7. SRP + SDD | 14. OHI + SRP + intensive maintenance | 21. SRP + CHX rinse + intensive maintenance |

INFLUENCE OF LONG TERM USE OF CHX RINSE

After removing the two trials that prescribed long-term use of CHX rinse (Llambés 2012 /2008 / 2005 and Santos 2013), this network meta-analysis included 33 trials with 29 treatments and 2614 patients. There was no evidence of inconsistency in the network (Figure A8.12).

As in the primary analysis, SRP showed a significant effect in reducing HbA1c relative to the control/no treatment group (mean difference was -0.38%; 95% CI: -0.71% to -0.08%). No significant difference was found between other periodontal therapies and SRP (Table 3.18).

TABLE 3.18 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITHOUT LONG TERM USE OF CHX RINSE AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.38* (0.16)	—								
3	0.00 (0.55)	-0.38 (0.53)	—							
4	0.12 (0.34)	-0.26 (0.30)	0.12 (0.53)	—						
5	0.29 (0.28)	-0.09 (0.29)	0.29 (0.60)	0.17 (0.41)	—					
6	0.09 (0.46)	-0.29 (0.49)	0.09 (0.72)	-0.03 (0.57)	-0.20 (0.54)	—				
7	-0.02 (0.47)	-0.40 (0.49)	-0.02 (0.72)	-0.14 (0.57)	-0.31 (0.55)	-0.11 (0.65)	—			
8	-0.16 (0.42)	-0.54 (0.45)	-0.16 (0.70)	-0.28 (0.54)	-0.45 (0.52)	-0.25 (0.62)	-0.14 (0.63)	—		
9	-0.14 (0.26)	-0.52 (0.30)	-0.14 (0.61)	-0.26 (0.42)	-0.43 (0.37)	-0.23 (0.52)	-0.12 (0.53)	0.02 (0.50)	—	
10	-0.21 (0.16)	-0.59* (0.21)	-0.21 (0.57)	-0.33 (0.36)	-0.50 (0.32)	-0.30 (0.49)	-0.19 (0.44)	-0.05 (0.45)	-0.07 (0.29)	—
11	-0.61 (0.48)	-0.98* (0.51)	-0.61 (0.73)	-0.73 (0.59)	-0.90 (0.56)	-0.70 (0.45)	-0.58 (0.67)	-0.45 (0.64)	-0.47 (0.54)	-0.40 (0.50)
12	-0.22 (0.79)	-0.60 (0.81)	-0.22 (0.98)	-0.34 (0.87)	-0.51 (0.85)	-0.31 (0.92)	-0.20 (0.93)	-0.06 (0.90)	-0.08 (0.84)	-0.01 (0.81)
13	-0.02	-0.40	-0.02	-0.14	-0.31	-0.11	0.00	0.14	0.12	0.19

	(0.31)	(0.35)	(0.63)	(0.46)	(0.42)	(0.55)	(0.56)	(0.53)	(0.40)	(0.35)
14	-0.14 (0.26)	-0.52 (0.30)	-0.14 (0.61)	-0.26 (0.42)	-0.43 (0.38)	-0.23 (0.53)	-0.12 (0.53)	0.02 (0.50)	0.00 (0.36)	0.07 (0.29)
15	-0.22 (0.27)	-0.60* (0.26)	-0.22 (0.59)	-0.34 (0.39)	-0.51 (0.27)	-0.31 (0.53)	-0.20 (0.54)	-0.06 (0.50)	-0.08 (0.34)	-0.01 (0.30)
16	-0.31 (0.35)	-0.69* (0.34)	-0.31 (0.63)	-0.43 (0.45)	-0.60 (0.40)	-0.40 (0.58)	-0.29 (0.58)	-0.15 (0.55)	-0.17 (0.42)	-0.10 (0.38)
17	-0.69 (0.36)	-1.06* (0.33)	-0.69 (0.62)	-0.81 (0.44)	-0.98* (0.44)	-0.78 (0.59)	-0.66 (0.59)	-0.53 (0.56)	-0.55 (0.44)	-0.48 (0.39)
18	0.22 (0.40)	-0.16 (0.42)	0.22 (0.68)	0.09 (0.52)	-0.08 (0.46)	0.13 (0.61)	0.24 (0.62)	0.38 (0.59)	0.36 (0.41)	0.43 (0.43)
19	-0.82 (0.64)	-1.20 (0.64)	-0.82 (0.83)	-0.95 (0.70)	-1.12 (0.64)	-0.91 (0.79)	-0.80 (0.79)	-0.66 (0.77)	-0.68 (0.67)	-0.61 (0.66)
20	0.68 (0.65)	0.30 (0.65)	0.68 (0.84)	0.56 (0.72)	0.39 (0.66)	0.59 (0.80)	0.70 (0.80)	0.84 (0.78)	0.82 (0.68)	0.89 (0.67)
21	0.60 (0.58)	0.22 (0.57)	0.60 (0.78)	0.48 (0.65)	0.31 (0.58)	0.51 (0.74)	0.62 (0.74)	0.76 (0.72)	0.74 (0.61)	0.81 (0.59)
22	-1.28 (0.77)	-1.66* (0.77)	-1.28 (0.93)	-1.40 (0.83)	-1.57* (0.78)	-1.37 (0.90)	-1.26 (0.91)	-1.12 (0.89)	-1.14 (0.80)	-1.07 (0.79)
23	0.02 (0.33)	-0.36 (0.29)	0.02 (0.61)	-0.10 (0.42)	-0.27 (0.41)	-0.07 (0.56)	0.04 (0.57)	0.18 (0.54)	0.16 (0.42)	0.23 (0.36)
24	-0.21 (0.34)	-0.58 (0.30)	-0.21 (0.44)	-0.33 (0.30)	-0.50 (0.41)	-0.30 (0.57)	-0.19 (0.57)	-0.05 (0.54)	-0.07 (0.42)	0.00 (0.36)
25	0.02 (0.29)	-0.36 (0.33)	0.02 (0.63)	-0.10 (0.44)	-0.27 (0.41)	-0.07 (0.54)	0.04 (0.56)	0.18 (0.52)	0.16 (0.39)	0.23 (0.33)
26	-0.01 (0.31)	-0.39 (0.35)	-0.01 (0.63)	-0.13 (0.46)	-0.30 (0.42)	-0.10 (0.55)	0.01 (0.56)	0.15 (0.53)	0.13 (0.41)	0.20 (0.35)
27	0.18 (0.38)	-0.20 (0.34)	0.18 (0.63)	0.06 (0.45)	-0.11 (0.44)	0.09 (0.59)	0.20 (0.60)	0.34 (0.57)	0.32 (0.45)	0.39 (0.40)
28	0.05 (0.68)	-0.33 (0.67)	0.05 (0.86)	-0.08 (0.73)	-0.25 (0.70)	-0.05 (0.82)	0.07 (0.82)	0.21 (0.79)	0.18 (0.71)	0.26 (0.69)
29	0.44 (0.36)	0.06 (0.32)	0.43 (0.62)	0.31 (0.44)	0.14 (0.43)	0.34 (0.58)	0.46 (0.58)	0.60 (0.56)	0.57 (0.44)	0.65 (0.38)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.39 (0.93)	—								
13	0.59 (0.57)	0.20 (0.85)	—							
14	0.46 (0.55)	0.08 (0.84)	-0.12 (0.40)	—						
15	0.38 (0.55)	0.00 (0.84)	-0.20 (0.41)	-0.08 (0.37)	—					
16	0.30 (0.60)	-0.09 (0.87)	-0.29 (0.47)	-0.17 (0.44)	-0.09 (0.33)	—				
17	-0.08 (0.60)	-0.46 (0.87)	-0.67 (0.48)	-0.54 (0.45)	-0.46 (0.42)	-0.38 (0.47)	—			
18	0.82 (0.62)	0.44 (0.90)	0.24 (0.51)	0.36 (0.48)	0.44 (0.42)	0.53 (0.51)	0.90 (0.53)	—		
19	-0.22 (0.80)	-0.60 (1.02)	-0.80 (0.71)	-0.68 (0.69)	-0.60 (0.58)	-0.51 (0.67)	-0.14 (0.72)	-1.04 (0.72)	—	
20	1.29 (0.81)	0.90 (1.03)	0.70 (0.72)	0.82 (0.70)	0.90 (0.60)	0.99 (0.68)	1.37 (0.73)	0.46 (0.73)	1.50 (0.84)	—
21	1.21 (0.76)	0.82 (0.98)	0.62 (0.65)	0.74 (0.63)	0.82 (0.51)	0.91 (0.61)	1.29 (0.66)	0.38 (0.66)	1.42 (0.77)	-0.08 (0.79)
22	-0.67 (0.91)	-1.06 (1.11)	-1.26 (0.83)	-1.14 (0.82)	-1.06 (0.73)	-0.97 (0.80)	-0.59 (0.84)	-1.50 (0.85)	-0.46 (0.43)	-1.96* (0.94)
23	0.63 (0.58)	0.24 (0.86)	0.04 (0.46)	0.16 (0.42)	0.24 (0.39)	0.33 (0.45)	0.70 (0.44)	-0.20 (0.51)	0.84 (0.70)	-0.66 (0.71)
24	0.40 (0.59)	0.01 (0.87)	-0.19 (0.46)	-0.07 (0.42)	0.01 (0.40)	0.10 (0.45)	0.48 (0.45)	-0.42 (0.52)	0.62 (0.70)	-0.89 (0.72)
25	0.63 (0.56)	0.24 (0.85)	0.04 (0.43)	0.16 (0.39)	0.24 (0.40)	0.33 (0.46)	0.71 (0.47)	-0.20 (0.50)	0.84 (0.70)	-0.66 (0.72)

26	0.60 (0.57)	0.21 (0.85)	0.01 (0.44)	0.13 (0.40)	0.21 (0.41)	0.30 (0.47)	0.68 (0.48)	-0.23 (0.51)	0.81 (0.71)	-0.69 (0.72)
27	0.79 (0.61)	0.40 (0.88)	0.20 (0.48)	0.32 (0.45)	0.40 (0.43)	0.49 (0.48)	0.86 (0.47)	-0.04 (0.54)	1.00 (0.72)	-0.50 (0.73)
28	0.65 (0.83)	0.27 (1.04)	0.06 (0.74)	0.19 (0.72)	0.27 (0.67)	0.35 (0.58)	0.73 (0.74)	-0.17 (0.77)	0.87 (0.89)	-0.63 (0.89)
29	1.04 (0.60)	0.66 (0.88)	0.45 (0.47)	0.58 (0.44)	0.66 (0.41)	0.74 (0.46)	1.12* (0.46)	0.22 (0.53)	1.26 (0.71)	-0.25 (0.73)
Treatment	21	22	23	24	25	26	27	28	29	
21	—									
22	-1.88* (0.89)	—								
23	-0.58 (0.65)	1.30 (0.83)	—							
24	-0.81 (0.65)	1.07 (0.83)	-0.23 (0.42)	—						
25	-0.58 (0.64)	1.30 (0.83)	0.00 (0.45)	0.23 (0.45)	—					
26	-0.61 (0.65)	1.27 (0.83)	-0.03 (0.45)	0.20 (0.46)	-0.03 (0.43)	—				
27	-0.42 (0.67)	1.46 (0.85)	0.16 (0.45)	0.39 (0.46)	0.16 (0.47)	0.19 (0.49)	—			
28	-0.55 (0.84)	1.33 (0.99)	0.03 (0.73)	0.25 (0.73)	0.03 (0.74)	0.05 (0.74)	-0.13 (0.75)	—		
29	-0.17 (0.66)	1.72* (0.84)	0.42 (0.44)	0.64 (0.44)	0.42 (0.46)	0.44 (0.47)	0.26 (0.47)	0.39 (0.74)	—	

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 16. SRP + non-intensive maintenance |
| 2. Control/no treatment | 17. OHI + SRP + intensive maintenance |
| 3. Intensive OHI | 18. SRP + SDD + intensive maintenance |
| 4. CHX rinse | 19. SRP + Doxy + intensive maintenance |
| 5. Supragingival cleaning | 20. SRP + AMX + intensive maintenance |
| 6. Supragingival cleaning + AZM | 21. SRP + MTZ + AMX + intensive maintenance |
| 7. Doxy | 22. SRP + Doxy + aPDT + intensive maintenance |
| 8. SRP + powered subgingival water irrigation | 23. SRP/flap surgery+ Tinidazole + Ampicillin |
| 9. SRP + SDD | 24. SRP + CHX rinse |
| 10. SRP + Doxy | 25. SRP + SMV gel |
| 11. SRP + AZM | 26. SRP + TET (topical) |
| 12. SRP + ALN | 27. SRP + TET (topical) + intensive maintenance |
| 13. SRP + Omega 3 + aspirin | 28. SRP + TET (topical) + non-intensive maintenance |
| 14. SRP + aPDT | 29. SRP + CHX rinse + intensive maintenance |
| 15. SRP + intensive maintenance | |

INFLUENCE OF FM-SRP

The network meta-analysis that included only partial mouth SRP had 24 trials, 21 treatments and 2170 patients. There was no evidence of inconsistency in the network (Figure A8.13).

Results were congruent with primary analysis (Table 3.19). SRP had a significant effect in reducing HbA1c (mean difference was -0.43%; 95% CI: -0.82% to -0.08%), while other periodontal therapies showed no significant differences with SRP.

TABLE 3.19 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.43* (0.19)	—									
3	0.18 (0.39)	-0.25 (0.35)	—								
4	0.17 (0.33)	-0.26 (0.35)	-0.01 (0.49)	—							
5	0.00 (0.51)	-0.43 (0.53)	-0.18 (0.64)	-0.17 (0.60)	—						
6	-0.25 (0.38)	-0.68 (0.41)	-0.43 (0.54)	-0.42 (0.46)	-0.25 (0.61)	—					
7	-0.20 (0.18)	-0.62* (0.24)	-0.37 (0.42)	-0.37 (0.37)	-0.20 (0.47)	0.05 (0.39)	—				
8	-0.18 (0.80)	-0.61 (0.82)	-0.35 (0.89)	-0.35 (0.87)	-0.18 (0.95)	0.07 (0.88)	0.02 (0.82)	—			
9	-0.02 (0.35)	-0.45 (0.40)	-0.20 (0.53)	-0.19 (0.49)	-0.02 (0.62)	0.23 (0.51)	0.18 (0.40)	0.16 (0.87)	—		
10	0.06 (0.60)	-0.37 (0.62)	-0.11 (0.71)	-0.11 (0.68)	0.06 (0.77)	0.31 (0.70)	0.26 (0.60)	0.24 (1.01)	0.08 (0.69)	—	
11	-0.48 (0.39)	-0.91* (0.41)	-0.66 (0.54)	-0.65* (0.33)	-0.48 (0.63)	-0.23 (0.45)	-0.29 (0.42)	-0.30 (0.89)	-0.46 (0.52)	-0.55 (0.70)	—
12	-0.63 (0.42)	-1.06* (0.38)	-0.81 (0.51)	-0.80 (0.51)	-0.63 (0.65)	-0.38 (0.56)	-0.44 (0.44)	-0.45 (0.90)	-0.61 (0.55)	-0.69 (0.73)	-0.15 (0.56)
13	0.09 (0.46)	-0.33 (0.49)	-0.08 (0.59)	-0.07 (0.50)	0.10 (0.67)	0.34 (0.46)	0.29 (0.48)	0.27 (0.92)	0.12 (0.57)	0.03 (0.75)	0.58 (0.48)
14	0.35 (0.66)	-0.08 (0.68)	0.18 (0.76)	0.18 (0.63)	0.35 (0.83)	0.60 (0.70)	0.55 (0.68)	0.53 (1.05)	0.37 (0.75)	0.29 (0.89)	0.84 (0.54)
15	0.06 (0.39)	-0.36 (0.34)	-0.11 (0.48)	-0.10 (0.49)	0.07 (0.63)	0.32 (0.53)	0.26 (0.41)	0.24 (0.89)	0.09 (0.53)	0.00 (0.71)	0.55 (0.53)
16	-0.15 (0.40)	-0.58 (0.35)	-0.33 (0.35)	-0.32 (0.50)	-0.15 (0.64)	0.10 (0.54)	0.04 (0.42)	0.03 (0.90)	-0.13 (0.53)	-0.22 (0.71)	0.33 (0.54)
17	0.02 (0.34)	-0.41 (0.39)	-0.16 (0.52)	-0.15 (0.48)	0.02 (0.61)	0.27 (0.51)	0.22 (0.38)	0.20 (0.87)	0.04 (0.49)	-0.04 (0.69)	0.50 (0.52)
18	-0.01 (0.36)	-0.43 (0.40)	-0.18 (0.53)	-0.18 (0.49)	-0.01 (0.62)	0.24 (0.52)	0.19 (0.40)	0.17 (0.87)	0.01 (0.50)	-0.07 (0.69)	0.48 (0.53)
19	0.23 (0.42)	-0.20 (0.38)	0.05 (0.52)	0.06 (0.52)	0.23 (0.66)	0.48 (0.56)	0.42 (0.45)	0.41 (0.91)	0.25 (0.55)	0.17 (0.73)	0.71 (0.56)
20	0.49 (0.41)	0.06 (0.36)	0.31 (0.50)	0.32 (0.51)	0.49 (0.65)	0.74 (0.54)	0.68 (0.43)	0.67 (0.89)	0.51 (0.54)	0.43 (0.72)	0.97 (0.55)
21	-0.02 (0.54)	-0.45 (0.51)	-0.20 (0.50)	-0.19 (0.62)	-0.02 (0.74)	0.23 (0.65)	0.18 (0.56)	0.16 (0.97)	0.00 (0.65)	-0.08 (0.81)	0.46 (0.65)
Treatment	12	13	14	15	16	17	18	19	20	21	
12	—										
13	0.73 (0.62)	—									
14	0.98 (0.77)	0.26 (0.72)	—								
15	0.70 (0.51)	-0.03 (0.59)	-0.29 (0.76)	—							
16	0.48 (0.51)	-0.25 (0.60)	-0.51 (0.76)	-0.22 (0.49)	—						
17	0.65 (0.54)	-0.07 (0.57)	-0.33 (0.75)	-0.05 (0.52)	0.17 (0.52)	—					
18	0.63 (0.55)	-0.10 (0.58)	-0.36 (0.75)	-0.07 (0.53)	0.15 (0.53)	-0.03 (0.49)	—				
19	0.86 (0.53)	0.13 (0.62)	-0.12 (0.78)	0.16 (0.51)	0.38 (0.52)	0.21 (0.54)	0.24 (0.56)	—			
20	1.12*	0.39	0.14	0.42	0.64	0.47	0.49	0.26	—		

	(0.52)	(0.60)	(0.77)	(0.50)	(0.50)	(0.53)	(0.54)	(0.52)			
21	0.61 (0.63)	-0.12 (0.70)	-0.37 (0.85)	-0.09 (0.61)	0.13 (0.36)	-0.04 (0.64)	-0.01 (0.65)	-0.25 (0.64)	-0.51 (0.62)	—	

* Statistically significant

**Legend:

- | | |
|---------------------------------|---|
| 1. SRP | 12. OHI + SRP + intensive maintenance |
| 2. Control/no treatment | 13. SRP + SDD + intensive maintenance |
| 3. CHX rinse | 14. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning | 15. SRP/flap surgery+ Tinidazole + Ampicillin |
| 5. Doxy | 16. SRP + CHX rinse |
| 6. SRP + SDD | 17. SRP + SMV gel |
| 7. SRP + Doxy | 18. SRP + TET (topical) |
| 8. SRP + ALN | 19. SRP + TET (topical) + intensive maintenance |
| 9. SRP + Omega 3 + aspirin | 20. SRP + CHX rinse + intensive maintenance |
| 10. SRP + aPDT | 21. SRP + CHX rinse + Doxy |
| 11. SRP + intensive maintenance | |

3.2.2 FRUCTOSAMINE

Only one trial (Llambés 2012/2008/ 2005) reported the outcome of fructosamine. It evaluated the effect of “SRP plus CHX rinse” with or without adjunctive systemic doxycycline in type 1 diabetic patients. The results showed no significant difference in fructosamine between the two treatments.

3.2.3 PERIODONTAL PROBING DEPTH (PPD)

3 months

Forty-two trials reported change in PPD as an outcome. Thirty-two trials informed the evidence network for HbA1c at 3 months. Ten trials were excluded for the following reasons: did not provide data at 3 month (Deo 2010; Lima 2004; Rocha 2001; Artese 2015); compared FMSRP with PMSRP (Santos 2012; Santos 2009) or treatments were not connected to the network (Macedo 2014; Mendonca 2012/Bezerra 2014; O'Connell 2008; Rodrigues 2003). This network meta-analysis included 26 treatments providing 42 comparisons involving 2519 participants. There was no evidence of inconsistency in the network (Figure A8.17).

The results showed that compared with control/no treatment and, separately, compared with intensive OHI, SRP could significantly improve PPD. Nine periodontal therapies had a significantly better effect than SRP (lower PPD) (Table 3.20-3.21).

The direct evidence (Figure 3.5) was congruent with both random- and fixed-effects models with one exception. Estimates from the direct evidence showed SRP plus systemic AZM had a significantly better effect than SRP. This is congruent with the estimate from the fixed-effects model but not random-effects model. Both DIC and total residual deviance suggested the random-effects model to be a better fit of the data (Table 3.22).

TABLE 3.20 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.38* (0.07)	—								
3	0.58* (0.23)	0.20 (0.22)	—							
4	0.19 (0.14)	-0.19 (0.13)	-0.39 (0.24)	—						
5	0.02 (0.18)	-0.36* (0.18)	-0.56* (0.29)	-0.17 (0.22)	—					
6	-0.10 (0.16)	-0.48* (0.18)	-0.68* (0.28)	-0.29 (0.22)	-0.12 (0.24)	—				
7	0.38 (0.27)	0.00 (0.28)	-0.20 (0.36)	0.19 (0.31)	0.36 (0.32)	0.48 (0.32)	—			
8	-0.44* (0.16)	-0.82* (0.14)	-1.02* (0.26)	-0.63* (0.19)	-0.46* (0.22)	-0.34 (0.23)	-0.82* (0.31)	—		
9	-0.07 (0.19)	-0.45* (0.20)	-0.65* (0.30)	-0.26 (0.24)	-0.09 (0.26)	0.03 (0.25)	-0.45 (0.33)	0.37 (0.24)	—	
10	-0.09 (0.12)	-0.48* (0.15)	-0.67* (0.26)	-0.29 (0.19)	-0.11 (0.22)	0.01 (0.20)	-0.47 (0.30)	0.34 (0.20)	-0.02 (0.23)	—
11	0.11 (0.09)	-0.27* (0.11)	-0.47 (0.25)	-0.08 (0.17)	0.09 (0.20)	0.21 (0.19)	-0.27 (0.26)	0.55* (0.18)	0.18 (0.21)	0.21 (0.15)
12	-0.30 (0.16)	-0.68* (0.18)	-0.88* (0.28)	-0.49* (0.22)	-0.32 (0.24)	-0.20 (0.16)	-0.68* (0.32)	0.14 (0.23)	-0.23 (0.25)	-0.21 (0.21)
13	-0.40* (0.16)	-0.78* (0.18)	-0.98* (0.28)	-0.59* (0.22)	-0.42 (0.24)	-0.30 (0.23)	-0.78* (0.32)	0.04 (0.23)	-0.33 (0.25)	-0.30 (0.21)
14	-0.90* (0.22)	-1.28* (0.23)	-1.48* (0.32)	-1.09* (0.26)	-0.92* (0.28)	-0.80* (0.27)	-1.28* (0.35)	-0.46 (0.27)	-0.83* (0.29)	-0.80* (0.25)
15	0.12 (0.16)	-0.26 (0.18)	-0.46 (0.28)	-0.07 (0.21)	0.10 (0.24)	0.22 (0.23)	-0.26 (0.30)	0.56* (0.22)	0.19 (0.25)	0.21 (0.21)
16	-0.96* (0.17)	-1.34* (0.15)	-1.54* (0.27)	-1.15* (0.20)	-0.98* (0.23)	-0.86* (0.24)	-1.34* (0.32)	-0.52* (0.21)	-0.89* (0.26)	-0.86* (0.21)
17	0.05 (0.11)	-0.34* (0.09)	-0.53* (0.20)	-0.14 (0.13)	0.03 (0.20)	0.15 (0.20)	-0.33 (0.29)	0.49* (0.17)	0.12 (0.22)	0.14 (0.17)
18	-1.30* (0.14)	-1.68* (0.16)	-1.88* (0.27)	-1.49* (0.20)	-1.32* (0.23)	-1.20* (0.21)	-1.68* (0.31)	-0.86* (0.21)	-1.23* (0.23)	-1.21* (0.19)
19	-0.73* (0.18)	-1.11* (0.19)	-1.31* (0.29)	-0.92* (0.23)	-0.75* (0.25)	-0.63* (0.24)	-1.11* (0.33)	-0.29 (0.24)	-0.66* (0.26)	-0.64* (0.22)
20	-0.27 (0.24)	-0.65* (0.25)	-0.85* (0.33)	-0.46 (0.28)	-0.29 (0.30)	-0.17 (0.29)	-0.65 (0.37)	0.17 (0.29)	-0.20 (0.30)	-0.17 (0.27)
21	-1.12* (0.40)	-1.50* (0.41)	-1.70* (0.46)	-1.31* (0.42)	-1.14* (0.43)	-1.02* (0.43)	-1.50* (0.48)	-0.68 (0.43)	-1.05* (0.44)	-1.02* (0.42)
22	-1.32* (0.34)	-1.70* (0.35)	-1.90* (0.41)	-1.51* (0.37)	-1.34* (0.38)	-1.22* (0.38)	-1.70* (0.44)	-0.88* (0.38)	-1.25* (0.39)	-1.22* (0.37)
23	-1.01* (0.18)	-1.40* (0.19)	-1.59* (0.29)	-1.20* (0.23)	-1.03* (0.25)	-0.91* (0.24)	-1.39* (0.33)	-0.57* (0.24)	-0.94* (0.26)	-0.92* (0.22)

24	0.09 (0.14)	-0.29* (0.16)	-0.49 (0.27)	-0.10 (0.21)	0.07 (0.23)	0.19 (0.21)	-0.29 (0.31)	0.53* (0.21)	0.16 (0.23)	0.19 (0.18)
25	-0.22 (0.23)	-0.60* (0.21)	-0.80* (0.31)	-0.41 (0.25)	-0.24 (0.28)	-0.12 (0.28)	-0.60 (0.35)	0.22 (0.25)	-0.15 (0.30)	-0.13 (0.26)
26	-0.04 (0.20)	-0.43* (0.19)	-0.62* (0.26)	-0.23 (0.22)	-0.06 (0.26)	0.06 (0.26)	-0.42 (0.34)	0.40 (0.24)	0.03 (0.28)	0.05 (0.24)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	-0.41* (0.19)	—								
13	-0.51* (0.19)	-0.10 (0.23)	—							
14	-1.01* (0.24)	-0.60* (0.27)	-0.50 (0.27)	—						
15	0.01 (0.16)	0.42 (0.23)	0.52* (0.23)	1.02* (0.27)	—					
16	-1.07* (0.19)	-0.66* (0.24)	-0.56* (0.24)	-0.06 (0.28)	-1.08* (0.23)	—				
17	-0.06 (0.14)	0.35 (0.20)	0.45* (0.20)	0.95* (0.25)	-0.07 (0.19)	1.00* (0.18)	—			
18	-1.41* (0.17)	-1.00* (0.22)	-0.90* (0.21)	-0.40 (0.26)	-1.42* (0.21)	-0.34 (0.22)	-1.35* (0.18)	—		
19	-0.84* (0.20)	-0.43 (0.24)	-0.33 (0.24)	0.17 (0.29)	-0.85* (0.24)	0.23 (0.25)	-0.78* (0.21)	0.57* (0.23)	—	
20	-0.38 (0.26)	0.03 (0.29)	0.13 (0.29)	0.63 (0.33)	-0.39 (0.29)	0.69* (0.29)	-0.31 (0.26)	1.03* (0.28)	0.46 (0.30)	—
21	-1.23* (0.41)	-0.82 (0.43)	-0.72 (0.43)	-0.22 (0.45)	-1.24* (0.43)	-0.16 (0.43)	-1.16* (0.41)	0.18 (0.42)	-0.39 (0.44)	-0.85 (0.47)
22	-1.43* (0.36)	-1.02* (0.38)	-0.92* (0.38)	-0.42 (0.41)	-1.44* (0.38)	-0.36 (0.38)	-1.37* (0.36)	-0.02 (0.37)	-0.59 (0.39)	-1.05* (0.41)
23	-1.12* (0.20)	-0.71* (0.24)	-0.61* (0.24)	-0.11 (0.28)	-1.13* (0.24)	-0.06 (0.25)	-1.06* (0.21)	0.29 (0.23)	-0.28 (0.25)	-0.75* (0.30)
24	-0.02 (0.17)	0.39 (0.22)	0.49* (0.22)	0.99* (0.26)	-0.03 (0.21)	1.05* (0.22)	0.05 (0.18)	1.39* (0.20)	0.82* (0.22)	0.36 (0.27)
25	-0.33 (0.24)	0.08 (0.28)	0.18 (0.28)	0.68* (0.32)	-0.34 (0.28)	0.73* (0.26)	-0.27 (0.23)	1.08* (0.27)	0.51 (0.29)	0.04 (0.33)
26	-0.15 (0.22)	0.26 (0.26)	0.36 (0.26)	0.86* (0.30)	-0.16 (0.26)	0.91* (0.25)	-0.09 (0.17)	1.26* (0.24)	0.69* (0.27)	0.22 (0.31)
Treatment	21	22	23	24	25	26				
21	—									
22	-0.20 (0.52)	—								
23	0.10 (0.43)	0.31 (0.39)	—							
24	1.21* (0.43)	1.41* (0.37)	1.11* (0.23)	—						
25	0.89 (0.46)	1.10* (0.41)	0.79* (0.29)	-0.32 (0.27)	—					
26	1.07* (0.45)	1.28* (0.40)	0.97* (0.27)	-0.14 (0.25)	0.18 (0.29)	—				

* Statistically significant

**Legend:

- | | | |
|---|---|---|
| 1. SRP | 11. SRP + Doxy | 21. SRP + ALN gel |
| 2. Control/no treatment | 12. SRP + AZM | 22. SRP + SMV gel |
| 3. Intensive OHI | 13. SRP + MTZ + AMX | 23. SRP + CLM gel |
| 4. CHX rinse | 14. SRP + Omega 3 + aspirin | 24. SRP + TET (topical) |
| 5. Supragingival cleaning | 15. SRP + aPDT | 25. SRP + TET (topical) + intensive maintenance |
| 6. Supragingival cleaning + AZM | 16. SRP/flap surgery+ Tinidazole + Ampicillin | 26. SRP + CHX rinse + Doxy |
| 7. Doxy | 17. SRP + CHX rinse | |
| 8. OHI + SRP | 18. SRP + SZ gel | |
| 9. SRP + powered subgingival water irrigation | 19. SRP + AV gel | |
| 10. SRP + SDD | 20. SRP + AZM gel | |

TABLE 3.21 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

T**	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	26
1																										
2																										
3																										
4																										
5																										
6																										
7																										
8																										
9																										
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21																										
22																										
23																										
24																										
25																										
26																										

T: treatment

**Legend: same as table 3.19

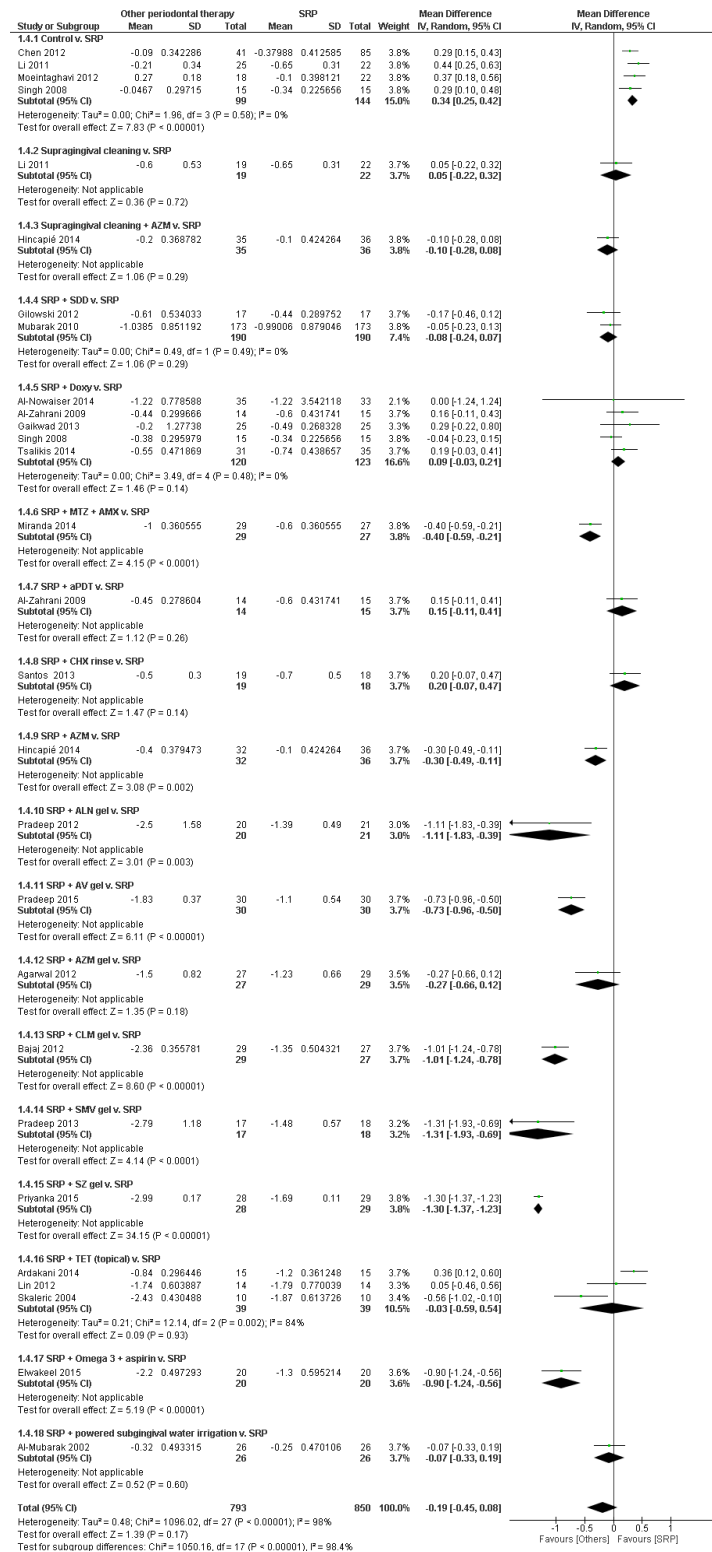
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.22 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PPD AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	0.34* (0.25 to 0.42)	4	0%	0.38* (0.24 to 0.54)	0.37* (0.29 to 0.45)
Supragingival cleaning	SRP	0.05 (-0.22 to 0.32)	1	NA	0.02 (-0.33 to 0.37)	0.01 (-0.25 to 0.27)
Supragingival cleaning + AZM	SRP	-0.10 (-0.28 to 0.08)	1	NA	-0.10 (-0.43 to 0.23)	-0.10 (-0.28 to 0.09)
SRP + SDD	SRP	-0.08 (-0.24 to 0.07)	2	0%	-0.09 (-0.35 to 0.15)	-0.08 (-0.24 to 0.07)
SRP + Doxy	SRP	0.09 (-0.03 to 0.21)	5	0%	0.11 (-0.06 to 0.30)	0.10 (-0.02 to 0.21)
SRP + MTZ + AMX	SRP	-0.40* (-0.59 to -0.21)	1	NA	-0.40* (-0.73 to -0.07)	-0.40* (-0.59 to -0.21)
SRP + aPDT	SRP	0.15 (-0.11 to 0.41)	1	NA	0.12 (-0.19 to 0.45)	0.11 (-0.10 to 0.32)
SRP + CHX rinse	SRP	0.20 (-0.07 to 0.47)	1	NA	0.05 (-0.15 to 0.28)	0.01 (-0.11 to 0.12)
SRP + AZM	SRP	-0.30* (-0.49 to -0.11)	1	NA	-0.30 (-0.63 to 0.03)	-0.30* (-0.49 to -0.11)
SRP + ALN gel	SRP	-1.11* (-1.83 to -0.39)	1	NA	-1.12* (-1.93 to -0.35)	-1.11* (-1.83 to -0.39)
SRP + AV gel	SRP	-0.73* (-0.96 to -0.50)	1	NA	-0.73* (-1.09 to -0.38)	-0.73* (-0.96 to -0.49)
SRP + AZM gel	SRP	-0.27 (-0.66 to 0.12)	1	NA	-0.27 (-0.74 to 0.20)	-0.27 (-0.67 to 0.12)
SRP + CLM gel	SRP	-1.01* (-1.24 to -0.78)	1	NA	-1.01* (-1.37 to -0.65)	-1.01* (-1.24 to -0.78)
SRP + SMV gel	SRP	-1.31* (-1.93 to -0.69)	1	NA	-1.32* (-2.00 to -0.66)	-1.31* (-1.94 to -0.69)
SRP + SZ gel	SRP	-1.30* (-1.37 to -1.23)	1	NA	-1.30* (-1.59 to -1.01)	-1.30* (-1.38 to -1.23)
SRP + TET (topical)	SRP	-0.03 (-0.59 to 0.54)	3	84%	0.09 (-0.20 to 0.34)	0.15 (-0.04 to 0.35)
SRP + Omega 3 + aspirin	SRP	-0.90* (-1.24 to -0.56)	1	NA	-0.90* (-1.33 to -0.46)	-0.90* (-1.24 to -0.56)
SRP + powered subgingival water irrigation	SRP	-0.07 (-0.33 to 0.19)	1	NA	-0.07 (-0.44 to 0.31)	-0.07 (-0.33 to 0.19)
DIC					-85.27	-83.39
Total residual deviance (Unconstrained data points)					71.81 (69 points)	79.52 (69 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.5 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PPD AT 3 MONTHS



SENSITIVITY ANALYSIS

INFLUENCE OF FM-SRP

The network meta-analysis that included only partial mouth SRP had 25 trials, 22 treatments and 2115 patients, providing 33 comparisons based on 21 trials with 2 arms and 4 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.18).

The results showed that compared to control/no treatment, SRP could significantly reduce PPD. Nine treatments had a significantly better effect than SRP. Interestingly, adjunctive use of topical TET caused a worse outcome than SRP applied alone (Table 3.23).

TABLE 3.23 PPD---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.38* (0.08)	—									
3	0.17 (0.13)	-0.21 (0.1)	—								
4	0.02 (0.16)	-0.36* (0.16)	-0.15 (0.19)	—							
5	0.39 (0.26)	0 (0.26)	0.21 (0.28)	0.36 (0.3)	—						
6	-0.44* (0.14)	-0.82* (0.11)	- 0.61* (0.15)	-0.46* (0.2)	-0.82* (0.29)	—					
7	-0.05 (0.14)	-0.43* (0.16)	-0.22 (0.19)	-0.07 (0.22)	-0.43 (0.29)	0.39* (0.19)	—				
8	0.11 (0.08)	-0.28* (0.1)	-0.06 (0.14)	0.08 (0.18)	-0.28 (0.24)	0.55* (0.15)	0.16 (0.16)	—			
9	-0.4* (0.14)	-0.78* (0.16)	- 0.57* (0.19)	-0.42 (0.21)	-0.78* (0.29)	0.04 (0.2)	-0.35 (0.2)	-0.51* (0.16)	—		
10	-0.9* (0.2)	-1.28* (0.22)	- 1.07* (0.24)	-0.92* (0.27)	-1.28* (0.33)	-0.46 (0.24)	-0.85* (0.25)	-1.01* (0.22)	-0.5* (0.25)	—	
11	0.12 (0.14)	-0.27 (0.16)	-0.05 (0.19)	0.09 (0.21)	-0.27 (0.28)	0.56* (0.19)	0.17 (0.2)	0.01 (0.14)	0.52* (0.2)	1.02* (0.25)	—
12	-0.96* (0.15)	-1.34* (0.13)	- 1.13* (0.16)	-0.98* (0.21)	-1.34* (0.29)	-0.52* (0.17)	-0.91* (0.2)	-1.07* (0.17)	-0.56* (0.21)	-0.06 (0.25)	-1.08* (0.21)
13	0.01 (0.12)	-0.38* (0.09)	-0.16 (0.11)	-0.02 (0.18)	-0.38 (0.28)	0.44* (0.14)	0.06 (0.18)	-0.1 (0.13)	0.41* (0.18)	0.91* (0.23)	-0.11 (0.18)
14	-1.3* (0.11)	-1.68* (0.14)	- 1.47* (0.17)	-1.32* (0.2)	-1.69* (0.28)	-0.86* (0.17)	-1.25* (0.18)	-1.41* (0.14)	-0.9* (0.18)	-0.4 (0.23)	-1.42* (0.18)

15	-0.73* (0.16)	-1.12* (0.18)	-0.9* (0.2)	-0.76* (0.23)	-1.12* (0.3)	-0.3 (0.21)	-0.68* (0.21)	-0.84* (0.18)	-0.33 (0.22)	0.16 (0.26)	-0.85* (0.21)
16	-0.27 (0.22)	-0.65* (0.24)	-0.44 (0.26)	-0.3 (0.28)	-0.66* (0.34)	0.17 (0.26)	-0.22 (0.27)	-0.38 (0.24)	0.13 (0.26)	0.63* (0.3)	-0.39 (0.27)
17	-1.11* (0.38)	-1.5* (0.39)	- 1.29* (0.4)	-1.14* (0.41)	-1.5* (0.46)	-0.68 (0.4)	-1.07* (0.41)	-1.22* (0.39)	-0.71 (0.41)	-0.22 (0.43)	-1.23* (0.41)
18	-1.29* (0.35)	-1.68* (0.35)	- 1.46* (0.37)	-1.32* (0.38)	-1.68* (0.42)	-0.85* (0.37)	-1.24* (0.37)	-1.4* (0.36)	-0.89* (0.38)	-0.39 (0.4)	-1.41* (0.38)
19	-1.01* (0.16)	-1.4* (0.18)	- 1.19* (0.2)	-1.04* (0.23)	-1.4* (0.3)	-0.58* (0.21)	-0.97* (0.21)	-1.12* (0.18)	-0.62* (0.21)	-0.12 (0.26)	-1.13* (0.21)
20	0.29* (0.14)	-0.09 (0.16)	0.12 (0.19)	0.27 (0.22)	-0.09 (0.29)	0.73* (0.2)	0.34 (0.2)	0.18 (0.16)	0.69* (0.2)	1.19* (0.25)	0.17 (0.2)
21	-0.22 (0.21)	-0.6* (0.2)	-0.39 (0.22)	-0.24 (0.26)	-0.6 (0.33)	0.22 (0.23)	-0.17 (0.25)	-0.33 (0.22)	0.18 (0.26)	0.68* (0.3)	-0.34 (0.26)
22	-0.08 (0.19)	-0.47* (0.17)	-0.25 (0.18)	-0.11 (0.24)	-0.47 (0.31)	0.35 (0.2)	-0.03 (0.23)	-0.19 (0.2)	0.32 (0.24)	0.82* (0.28)	-0.2 (0.23)
Treatment	12	13	14	15	16	17	18	19	20	21	22
12	—										
13	0.97* (0.15)	—									
14	-0.34 (0.19)	-1.31* (0.16)	—								
15	0.23 (0.22)	-0.74* (0.2)	0.57* (0.19)	—							
16	0.69* (0.27)	-0.28 (0.25)	1.03* (0.25)	0.46 (0.27)	—						
17	-0.16 (0.41)	-1.12* (0.4)	0.19 (0.4)	-0.38 (0.42)	-0.84 (0.44)	—					
18	-0.33 (0.38)	-1.3* (0.36)	0.01 (0.36)	-0.56 (0.38)	-1.02* (0.4)	-0.18 (0.52)	—				
19	-0.06 (0.22)	-1.02* (0.19)	0.29 (0.19)	-0.28 (0.22)	-0.74* (0.27)	0.1 (0.42)	0.28 (0.38)	—			
20	1.25* (0.2)	0.29 (0.18)	1.59* (0.18)	1.03* (0.21)	0.56* (0.26)	1.41* (0.4)	1.58* (0.38)	1.31* (0.21)	—		
21	0.74* (0.24)	-0.23 (0.22)	1.08* (0.24)	0.51* (0.26)	0.05 (0.31)	0.89* (0.44)	1.07* (0.4)	0.8* (0.26)	-0.51 (0.26)	—	
22	0.88* (0.21)	-0.09 (0.15)	1.22* (0.22)	0.65* (0.25)	0.19 (0.29)	1.03* (0.43)	1.21* (0.39)	0.93* (0.25)	-0.37 (0.23)	0.14 (0.26)	—

* Statistically significant

**Legend:

- | | |
|-----------------------------|---|
| 1. SRP | 12. SRP/flap surgery+ Tinidazole + Ampicillin |
| 2. Control/no treatment | 13. SRP + CHX rinse |
| 3. CHX rinse | 14. SRP + SZ gel |
| 4. Supragingival cleaning | 15. SRP + AV gel |
| 5. Doxy | 16. SRP + AZM gel |
| 6. OHI + SRP | 17. SRP + ALN gel |
| 7. SRP + SDD | 18. SRP + SMV gel |
| 8. SRP + Doxy | 19. SRP + CLM gel |
| 9. SRP + MTZ + AMX | 20. SRP + TET (topical) |
| 10. SRP + Omega 3 + aspirin | 21. SRP + TET (topical) + intensive maintenance |
| 11. SRP + aPDT | 22. SRP + CHX rinse + Doxy |

End of study

This network meta-analysis was based on data at the end of the studies. It included 39 trials, 36 treatment and 2715 patients. 3 trials that reported the outcome of PPD were not included. Two of them compared FMSRP with PMSRP (Santos 2012; Santos 2009)

and the other one (Mendonca 2012/Bezerra 2014) was not connected to the network.

There was no evidence of inconsistency in the network (Figure A8.20).

Compared to control/no treatment, SRP could significantly reduce PPD by end of study. Twelve periodontal therapies showed a significantly better effect than SRP (lower PPD) (Table 3.24-3.25). Results from both random- and fixed-effects models were congruent with direct evidence (Figure 3.6) with one exception. An estimate from the fixed effect model showed “SRP plus topical TET” was significantly worse than SRP alone, which is not consistent with other estimates (Table 3.26).

TABLE 3.24 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treat ment **	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	0.42* (0.10)	—										
3	0.51 (0.30)	0.09 (0.29)	—									
4	0.19 (0.20)	-0.23 (0.17)	-0.32 (0.29)	—								
5	0.17 (0.19)	-0.25 (0.19)	-0.34 (0.34)	-0.02 (0.25)	—							
6	0.10 (0.20)	-0.32 (0.22)	-0.41 (0.36)	-0.09 (0.28)	-0.07 (0.27)	—						
7	0.31 (0.29)	-0.11 (0.30)	-0.20 (0.41)	0.12 (0.35)	0.14 (0.34)	0.22 (0.35)	—					
8	-0.07 (0.21)	-0.49* (0.24)	-0.58 (0.37)	-0.26 (0.29)	-0.23 (0.29)	-0.16 (0.29)	-0.38 (0.36)	—				
9	-0.32* (0.13)	-0.74* (0.16)	-0.83* (0.32)	-0.51* (0.23)	-0.49* (0.22)	-0.42 (0.23)	-0.64* (0.31)	-0.26 (0.25)	—			
10	0.03 (0.10)	-0.38* (0.13)	-0.47 (0.31)	-0.15 (0.21)	-0.13 (0.21)	-0.06 (0.22)	-0.28 (0.27)	0.10 (0.23)	0.36* (0.16)	—		
11	-0.20 (0.20)	-0.62* (0.22)	-0.71 (0.36)	-0.39 (0.28)	-0.37 (0.27)	-0.30 (0.20)	-0.51 (0.35)	-0.13 (0.29)	0.12 (0.23)	-0.24 (0.22)	—	
12	-0.43 (0.27)	-0.85* (0.29)	-0.93* (0.41)	-0.62 (0.34)	-0.59 (0.33)	-0.52 (0.34)	-0.74 (0.40)	-0.36 (0.34)	-0.10 (0.30)	-0.46 (0.29)	-0.23 (0.34)	—
13	-0.84* (0.24)	-1.26* (0.26)	-1.35* (0.39)	-1.03* (0.31)	-1.01* (0.31)	-0.94* (0.31)	-1.16* (0.38)	-0.78* (0.32)	-0.52* (0.27)	-0.88* (0.26)	-0.64* (0.31)	-0.42 (0.37)
14	0.07 (0.18)	-0.35 (0.20)	-0.43 (0.35)	-0.12 (0.26)	-0.09 (0.26)	-0.02 (0.27)	-0.24 (0.33)	0.14 (0.28)	0.40 (0.22)	0.04 (0.18)	0.27 (0.27)	0.50 (0.33)
15	-0.10 (0.16)	-0.52* (0.14)	-0.60 (0.32)	-0.29 (0.22)	-0.26 (0.23)	-0.19 (0.25)	-0.41 (0.32)	-0.03 (0.26)	0.23 (0.18)	-0.13 (0.18)	0.10 (0.25)	0.33 (0.32)
16	-0.04 (0.20)	-0.46 (0.17)	-0.55 (0.33)	-0.23 (0.24)	-0.20 (0.26)	-0.13 (0.28)	-0.35 (0.34)	0.03 (0.29)	0.29 (0.23)	-0.07 (0.21)	0.16 (0.28)	0.39 (0.34)
17	-0.45* (0.20)	-0.87* (0.17)	-0.96* (0.33)	-0.64* (0.24)	-0.62* (0.26)	-0.55 (0.28)	-0.76* (0.35)	-0.39 (0.29)	-0.13 (0.23)	-0.49* (0.21)	-0.25 (0.28)	-0.03 (0.34)
18	-0.37 (0.26)	-0.79* (0.27)	-0.88* (0.39)	-0.56 (0.32)	-0.54 (0.31)	-0.47 (0.33)	-0.68 (0.39)	-0.31 (0.33)	-0.05 (0.26)	-0.41 (0.27)	-0.17 (0.32)	0.05 (0.38)
19	-0.39 (0.28)	-0.81* (0.27)	-0.90* (0.39)	-0.58 (0.32)	-0.56 (0.33)	-0.49 (0.34)	-0.70 (0.40)	-0.32 (0.35)	-0.07 (0.30)	-0.43 (0.30)	-0.19 (0.34)	0.03 (0.40)
20	0.00	-0.42	-0.51	-0.19	-0.17	-0.10	-0.31	0.06	0.32	-0.04	0.20	0.42

	(0.29)	(0.28)	(0.39)	(0.32)	(0.33)	(0.34)	(0.40)	(0.36)	(0.30)	(0.30)	(0.35)	(0.40)
21	-0.49 (0.25)	-0.91* (0.24)	-1.00* (0.37)	-0.68* (0.29)	-0.66* (0.30)	-0.59 (0.31)	-0.81* (0.37)	-0.43 (0.32)	-0.17 (0.26)	-0.53* (0.26)	-0.29 (0.31)	-0.07 (0.37)
22	-0.38 (0.34)	-0.80* (0.34)	-0.89* (0.44)	-0.57 (0.37)	-0.55 (0.38)	-0.48 (0.39)	-0.69 (0.45)	-0.31 (0.40)	-0.06 (0.36)	-0.42 (0.36)	-0.18 (0.39)	0.04 (0.44)
23	-0.92* (0.21)	-1.34* (0.18)	-1.43* (0.34)	-1.11* (0.25)	-1.09* (0.26)	-1.02* (0.29)	-1.24* (0.36)	-0.86* (0.30)	-0.60* (0.24)	-0.96* (0.22)	-0.72* (0.29)	-0.50 (0.34)
24	-0.02 (0.20)	-0.44* (0.17)	-0.53* (0.23)	-0.21 (0.18)	-0.19 (0.26)	-0.12 (0.28)	-0.33 (0.35)	0.05 (0.29)	0.30 (0.23)	-0.06 (0.22)	0.18 (0.28)	0.41 (0.34)
25	-2.48* (0.42)	-2.90* (0.43)	-2.98* (0.52)	-2.67* (0.46)	-2.64* (0.46)	-2.57* (0.47)	-2.79* (0.52)	-2.41* (0.47)	-2.15* (0.44)	-2.51* (0.43)	-2.28* (0.47)	-2.05* (0.51)
26	-0.97* (0.21)	-1.39* (0.23)	-1.48* (0.37)	-1.16* (0.29)	-1.14* (0.29)	-1.07* (0.29)	-1.28* (0.36)	-0.90* (0.30)	-0.65* (0.25)	-1.01* (0.23)	-0.77* (0.29)	-0.55 (0.34)
27	-2.64* (0.17)	-3.06* (0.20)	-3.15* (0.35)	-2.83* (0.26)	-2.81* (0.25)	-2.74* (0.26)	-2.95* (0.34)	-2.57* (0.27)	-2.32* (0.21)	-2.68* (0.20)	-2.44* (0.26)	-2.21* (0.32)
28	-0.74* (0.22)	-1.16* (0.25)	-1.25* (0.38)	-0.93* (0.30)	-0.91* (0.29)	-0.84* (0.30)	-1.05* (0.37)	-0.67* (0.31)	-0.42 (0.26)	-0.78* (0.24)	-0.54 (0.30)	-0.31 (0.35)
29	-0.67* (0.31)	-1.09* (0.33)	-1.18* (0.43)	-0.86* (0.37)	-0.84* (0.36)	-0.77* (0.37)	-0.98* (0.42)	-0.60 (0.38)	-0.35 (0.34)	-0.71* (0.33)	-0.47 (0.37)	-0.24 (0.42)
30	-2.20* (0.44)	-2.62* (0.45)	-2.71* (0.53)	-2.39* (0.48)	-2.36* (0.48)	-2.29* (0.48)	-2.51* (0.52)	-2.13* (0.49)	-1.87* (0.45)	-2.23* (0.45)	-2.00* (0.48)	-1.77* (0.52)
31	0.26 (0.17)	-0.16 (0.20)	-0.24 (0.35)	0.07 (0.26)	0.10 (0.26)	0.17 (0.26)	-0.05 (0.34)	0.33 (0.27)	0.59 (0.22)	0.23 (0.20)	0.46 (0.26)	0.69* (0.32)
32	-0.18 (0.26)	-0.60* (0.24)	-0.69 (0.37)	-0.37 (0.29)	-0.35 (0.31)	-0.27 (0.32)	-0.49 (0.38)	-0.11 (0.33)	0.15 (0.28)	-0.21 (0.27)	0.02 (0.33)	0.25 (0.38)
33	-1.13* (0.37)	-1.55* (0.36)	-1.64* (0.46)	-1.32* (0.39)	-1.30* (0.40)	-1.23* (0.42)	-1.45* (0.47)	-1.07* (0.42)	-0.81* (0.39)	-1.17* (0.38)	-0.93* (0.42)	-0.71 (0.46)
34	0.20 (0.17)	-0.22 (0.15)	-0.31 (0.32)	0.01 (0.22)	0.03 (0.23)	0.10 (0.26)	-0.11 (0.33)	0.27 (0.27)	0.52* (0.20)	0.16 (0.19)	0.40 (0.26)	0.62 (0.32)
35	-2.20* (0.38)	-2.62* (0.37)	-2.71* (0.47)	-2.39* (0.40)	-2.36* (0.41)	-2.29* (0.42)	-2.51* (0.47)	-2.13* (0.43)	-1.87* (0.39)	-2.23* (0.38)	-2.00* (0.42)	-1.77* (0.46)
36	-0.11 (0.28)	-0.53* (0.26)	-0.62* (0.30)	-0.30 (0.26)	-0.28 (0.32)	-0.20 (0.34)	-0.42 (0.40)	-0.04 (0.35)	0.22 (0.30)	-0.14 (0.29)	0.09 (0.34)	0.32 (0.39)
Treat ment	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	0.92* (0.31)	—										
15	0.75* (0.29)	-0.17 (0.24)	—									
16	0.81* (0.31)	-0.11 (0.26)	0.06 (0.18)	—								
17	0.39 (0.31)	-0.53 (0.27)	-0.36 (0.22)	-0.41 (0.24)	—							
18	0.47 (0.35)	-0.45 (0.32)	-0.28 (0.28)	-0.33 (0.31)	0.08 (0.32)	—						
19	0.45 (0.37)	-0.47 (0.34)	-0.30 (0.24)	-0.35 (0.30)	0.06 (0.32)	-0.02 (0.36)	—					
20	0.84* (0.38)	-0.08 (0.33)	0.09 (0.24)	0.03 (0.30)	0.45 (0.32)	0.37 (0.37)	0.39 (0.34)	—				
21	0.35 (0.34)	-0.57 (0.30)	-0.40* (0.19)	-0.46 (0.26)	-0.04 (0.29)	-0.12 (0.34)	-0.10 (0.30)	-0.49 (0.30)	—			
22	0.46 (0.42)	-0.46 (0.39)	-0.29 (0.31)	-0.34 (0.35)	0.07 (0.38)	-0.01 (0.42)	0.01 (0.19)	-0.38 (0.39)	0.11 (0.36)	—		
23	-0.08 (0.32)	-1.00* (0.27)	-0.83* (0.23)	-0.89* (0.25)	-0.47 (0.25)	-0.55 (0.32)	-0.53 (0.33)	-0.92* (0.33)	-0.43 (0.30)	-0.54 (0.38)	—	
24	0.82* (0.31)	-0.09 (0.27)	0.08 (0.22)	0.02 (0.24)	0.43 (0.24)	0.35 (0.32)	0.37 (0.32)	-0.02 (0.32)	0.47 (0.29)	0.36 (0.38)	0.90* (0.25)	—
25	-1.63* (0.48)	-2.55* (0.46)	-2.38* (0.45)	-2.44* (0.46)	-2.02* (0.46)	-2.10* (0.48)	-2.08* (0.50)	-2.47* (0.51)	-1.98* (0.49)	-2.09* (0.54)	-1.55* (0.47)	-2.46* (0.47)
26	-0.13 (0.31)	-1.05* (0.28)	-0.88* (0.26)	-0.93* (0.29)	-0.52 (0.29)	-0.60 (0.33)	-0.58 (0.35)	-0.97* (0.36)	-0.48 (0.32)	-0.59 (0.40)	-0.05 (0.30)	-0.95* (0.29)
27	-1.80* (0.29)	-2.71* (0.25)	-2.54* (0.23)	-2.60* (0.26)	-2.19* (0.26)	-2.27* (0.31)	-2.25* (0.33)	-2.64* (0.33)	-2.15* (0.30)	-2.26* (0.38)	-1.72* (0.27)	-2.62* (0.26)

28	0.10 (0.33)	-0.81* (0.29)	-0.64* (0.27)	-0.70* (0.30)	-0.29 (0.30)	-0.37 (0.34)	-0.35 (0.36)	-0.74* (0.36)	-0.25 (0.33)	-0.36 (0.41)	0.18 (0.30)	-0.72* (0.30)
29	0.17 (0.39)	-0.74* (0.36)	-0.57 (0.35)	-0.63 (0.37)	-0.22 (0.37)	-0.30 (0.41)	-0.28 (0.43)	-0.67 (0.42)	-0.18 (0.40)	-0.29 (0.47)	0.25 (0.38)	-0.65 (0.37)
30	-1.35* (0.50)	-2.27* (0.47)	-2.10* (0.46)	-2.16* (0.48)	-1.74* (0.48)	-1.82* (0.51)	-1.81* (0.52)	-2.19* (0.51)	-1.70* (0.50)	-1.82* (0.56)	-1.27* (0.48)	-2.18* (0.48)
31	1.11* (0.29)	0.19 (0.25)	0.36 (0.23)	0.30 (0.26)	0.72* (0.26)	0.64* (0.31)	0.66 (0.33)	0.27 (0.34)	0.76* (0.30)	0.65 (0.39)	1.19* (0.27)	0.28 (0.27)
32	0.67 (0.35)	-0.25 (0.27)	-0.08 (0.27)	-0.14 (0.29)	0.27 (0.29)	0.19 (0.35)	0.21 (0.36)	-0.18 (0.37)	0.32 (0.33)	0.20 (0.41)	0.75* (0.29)	-0.16 (0.29)
33	-0.29 (0.44)	-1.21* (0.41)	-1.04* (0.36)	-1.10* (0.32)	-0.68 (0.40)	-0.76 (0.45)	-0.74 (0.43)	-1.13* (0.44)	-0.64 (0.41)	-0.75 (0.47)	-0.21 (0.40)	-1.11* (0.39)
34	1.04* (0.30)	0.12 (0.25)	0.29 (0.16)	0.24 (0.21)	0.65* (0.22)	0.57 (0.30)	0.59* (0.28)	0.20 (0.29)	0.69* (0.25)	0.58 (0.34)	1.12* (0.23)	0.22 (0.23)
35	-1.35* (0.45)	-2.27* (0.42)	-2.10* (0.34)	-2.16* (0.38)	-1.74* (0.40)	-1.82* (0.44)	-1.80* (0.41)	-2.19* (0.42)	-1.70* (0.39)	-1.81* (0.46)	-1.27* (0.41)	-2.18* (0.41)
36	0.74* (0.37)	-0.18 (0.33)	-0.01 (0.29)	-0.07 (0.31)	0.34 (0.31)	0.26 (0.37)	0.28 (0.38)	-0.11 (0.38)	0.39 (0.35)	0.27 (0.42)	0.81* (0.32)	-0.09 (0.19)
Treat ment	25	26	27	28	29	30	31	32	33	34	35	36
25	—											
26	1.50* (0.46)	—										
27	-0.16 (0.45)	-1.67* (0.27)	—									
28	1.74* (0.47)	0.23 (0.31)	1.90* (0.28)	—								
29	1.81* (0.53)	0.30 (0.38)	1.97* (0.36)	0.07 (0.38)	—							
30	0.28 (0.62)	-1.22* (0.49)	0.44 (0.47)	-1.46* (0.49)	-1.53* (0.53)	—						
31	2.74* (0.45)	1.24* (0.27)	2.90* (0.24)	1.00* (0.28)	0.93* (0.36)	2.46* (0.47)	—					
32	2.30* (0.49)	0.79* (0.33)	2.46* (0.31)	0.56 (0.34)	0.49 (0.41)	2.02* (0.51)	-0.44 (0.31)	—				
33	1.34* (0.56)	-0.16 (0.42)	1.51* (0.41)	-0.39 (0.43)	-0.46 (0.48)	1.06 (0.58)	-1.40* (0.41)	-0.95* (0.43)	—			
34	2.67* (0.45)	1.17* (0.27)	2.84* (0.24)	0.94* (0.28)	0.87* (0.36)	2.40* (0.47)	-0.07 (0.25)	0.38 (0.28)	1.33* (0.38)	—		
35	0.28 (0.56)	-1.22* (0.43)	0.44 (0.41)	-1.46* (0.44)	-1.53* (0.49)	0.00 (0.57)	-2.46* (0.41)	-2.02* (0.43)	-1.06* (0.49)	-2.40* (0.38)	—	
36	2.37* (0.51)	0.86* (0.35)	2.53* (0.32)	0.63 (0.36)	0.56 (0.42)	2.09* (0.52)	-0.37 (0.33)	0.07 (0.35)	1.03* (0.44)	-0.31 (0.30)	2.09* (0.45)	—

* Statistically significant

**Legend:

1. SRP
2. Control/no treatment
3. Intensive OHI
4. CHX rinse
5. Supragingival cleaning
6. Supragingival cleaning + AZM
7. Doxy
8. SRP + powered subgingival water irrigation
9. SRP + SDD
10. SRP + Doxy
11. SRP + AZM
12. SRP + ALN
13. SRP + Omega 3 + aspirin
14. SRP + aPDT
15. SRP + intensive maintenance
16. SRP + non-intensive maintenance
17. OHI+ SRP+ intensive maintenance
18. SRP + SDD + intensive maintenance
19. SRP + Doxy+ intensive maintenance
20. SRP + AMX+ intensive maintenance
21. SRP + MTZ + AMX + intensive maintenance
22. SRP+ Doxy+ aPDT + intensive maintenance
23. SRP/flap surgery+ Tinidazole + Ampicillin
24. SRP + CHX rinse
25. SRP + SMV gel
26. SRP + CLM gel
27. SRP + SZ gel
28. SRP + AV gel
29. SRP + AZM gel
30. SRP + ALN gel
31. SRP + TET (topical)
32. SRP + TET (topical) + intensive maintenance
33. SRP + TET (topical) + non-intensive maintenance
34. SRP + CHX rinse + intensive maintenance
35. SRP + Doxy gel+ intensive maintenance
36. SRP + CHX rinse + Doxy

TABLE 3.25 PPD ---- HEAD-TO-HEAD CPMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

[illegible]

T: treatment

**Legend: same as table 3.23

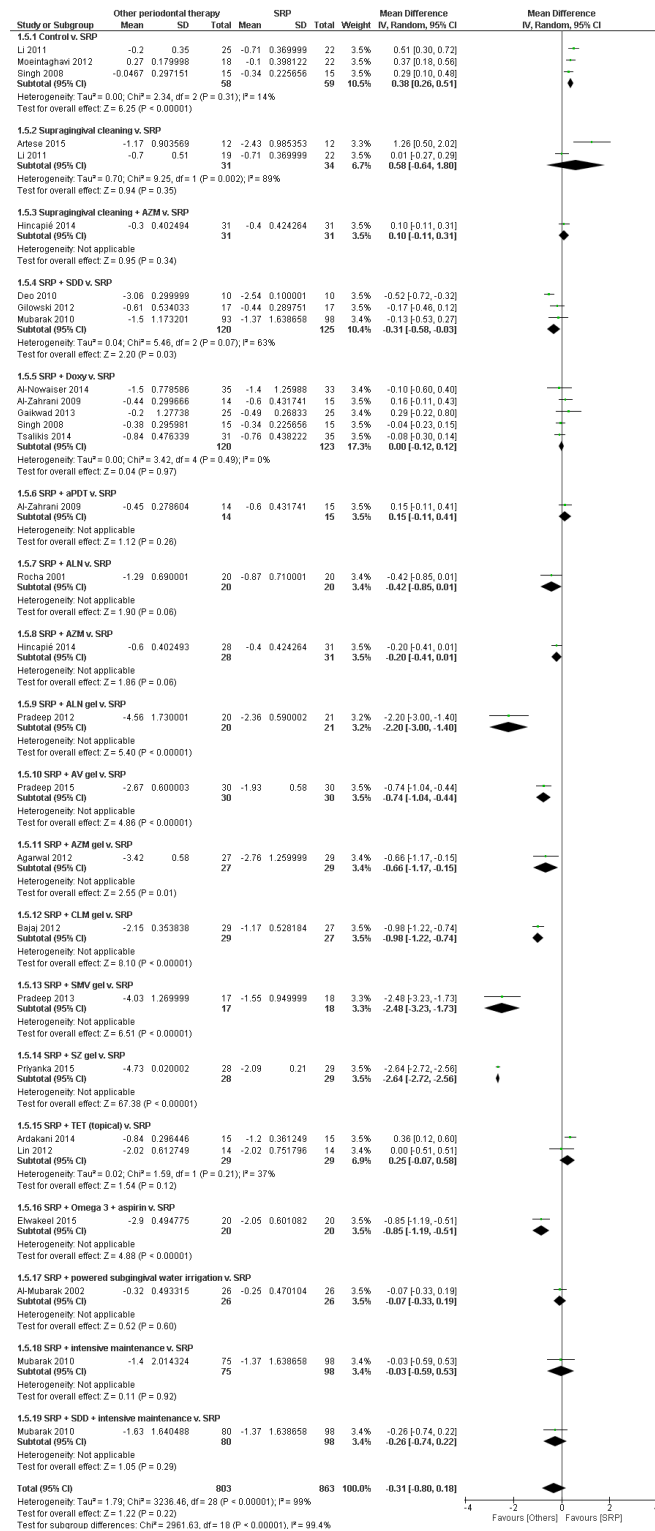
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.26 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PPD AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	0.38* (0.26 to 0.51)	3	14%	0.42* (0.22 to 0.64)	0.40* (0.29 to 0.51)
Supragingival cleaning	SRP	0.58 (-0.64 to 1.80)	2	89%	0.17 (-0.16 to 0.60)	0.08 (-0.17 to 0.32)
Supragingival cleaning + AZM	SRP	0.10 (-0.11 to 0.31)	1	NA	0.10 (-0.30 to 0.50)	0.10 (-0.11 to 0.31)
SRP + SDD	SRP	-0.31* (-0.58 to -0.03)	3	63%	-0.32* (-0.56 to -0.05)	-0.37* (-0.51 to -0.22)
SRP + Doxy	SRP	0.00 (-0.12 to 0.12)	5	0%	0.03 (-0.16 to 0.24)	0.02 (-0.10 to 0.13)
SRP + aPDT	SRP	0.15 (-0.11 to 0.41)	1	NA	0.07 (-0.28 to 0.45)	0.05 (-0.16 to 0.26)
SRP + ALN	SRP	-0.42 (-0.85 to 0.01)	1	NA	-0.43 (-0.97 to 0.12)	-0.42 (-0.86 to 0.01)
SRP + AZM	SRP	-0.20 (-0.41 to 0.01)	1	NA	-0.20 (-0.60 to 0.20)	-0.20 (-0.41 to 0.01)
SRP + ALN gel	SRP	-2.20* (-3.00 to -1.40)	1	NA	-2.20* (-3.04 to -1.33)	-2.20* (-3.01 to -1.39)
SRP + AV gel	SRP	-0.74* (-1.04 to -0.44)	1	NA	-0.74* (-1.18 to -0.29)	-0.74* (-1.04 to -0.44)
SRP + AZM gel	SRP	-0.66* (-1.17 to -0.15)	1	NA	-0.67* (-1.27 to -0.05)	-0.66* (-1.17 to -0.15)
SRP + CLM gel	SRP	-0.98* (-1.22 to -0.74)	1	NA	-0.97* (-1.39 to -0.56)	-0.98* (-1.22 to -0.74)
SRP + SMV gel	SRP	-2.48* (-3.23 to -1.73)	1	NA	-2.48* (-3.29 to -1.66)	-2.48* (-3.24 to -1.73)
SRP + SZ gel	SRP	-2.64* (-2.72 to -2.56)	1	NA	-2.64* (-3.00 to -2.28)	-2.64* (-2.72 to -2.57)
SRP + TET (topical)	SRP	0.25 (-0.07 to 0.58)	2	37%	0.26 (-0.09 to 0.58)	0.30* (0.08 to 0.51)
SRP + Omega 3 + aspirin	SRP	-0.85* (-1.19 to -0.51)	1	NA	-0.84* (-1.33 to -0.37)	-0.85* (-1.19 to -0.51)
SRP + powered subgingival water irrigation	SRP	-0.07 (-0.33 to 0.19)	1	NA	-0.07 (-0.49 to 0.35)	-0.07 (-0.33 to 0.19)
SRP + intensive maintenance	SRP	-0.03 (-0.59 to 0.53)	1	NA	-0.10 (-0.40 to 0.23)	-0.10 (-0.27 to 0.07)
SRP + SDD + intensive maintenance	SRP	-0.26 (-0.74 to 0.22)	1	NA	-0.37 (-0.89 to 0.14)	-0.40 (-0.81 to 0.01)
DIC					-83.33	-81.11
Total residual deviance (Unconstrained data points)					91.11 (86 points)	99.29 (86 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.6 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PPD AT END OF STUDY



3.2.4 CLINICAL ATTACHMENT LEVEL (CAL)

3 months

Forty trials have reported CAL as an outcome. Ten were not included in this network for the following reasons: did not provide data at 3 month (Deo 2010; Lima 2004; Rocha 2001; Artese 2015); compared FMSRP with PMSRP (Santos 2012; Santos 2009) or treatments were not connected to the network (Macedo 2014; Mendonca 2012/Bezerra 2014; O'Connell 2008; Rodrigues 2003). There was no evidence of inconsistency in the network (Figure A8.22).

The network meta-analysis informing the effect of periodontal therapy on CAL at 3 months included 30 trials and 24 different therapies, providing 38 comparisons.

Compared to control/no treatment, SRP had a significant effect on improving the CAL. Three therapies showed a significantly better effect than SRP (Table 3.27-3.28). Direct evidence (Figure 3.7) was not consistent with the mixed evidence. Previous trials suggested “SRP plus topical AV gel” and “SRP plus topical CLM gel” were significantly better than SRP alone. These differences existed in the fixed-effect model but not in the random-effects model. Compared with SRP, SRP plus CHX rinse showed a significantly worse effect in the fixed-effects model. Based on DIC and total residual deviance, the random-effect model appears to be a better fit (Table 3.29).

TABLE 3.27 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	0.48* (0.12)	—										
3	0.59 (0.39)	0.11 (0.39)	—									
4	0.14 (0.26)	-0.34 (0.25)	-0.45 (0.46)	—								
5	0.01 (0.30)	-0.47 (0.33)	-0.58 (0.50)	-0.14 (0.40)	—							
6	0.20 (0.66)	-0.28 (0.67)	-0.40 (0.77)	0.05 (0.71)	0.19 (0.73)	—						
7	-0.25 (0.29)	-0.73* (0.26)	-0.84 (0.47)	-0.39 (0.36)	-0.26 (0.42)	-0.45 (0.72)	—					
8	0.12 (0.33)	-0.36 (0.36)	-0.47 (0.51)	-0.02 (0.42)	0.11 (0.45)	-0.08 (0.75)	0.37 (0.44)	—				
9	-0.01 (0.23)	-0.49 (0.27)	-0.61 (0.45)	-0.16 (0.35)	-0.02 (0.38)	-0.21 (0.71)	0.24 (0.37)	-0.13 (0.41)	—			
10	0.06	-0.42*	-0.54	-0.09	0.05	-0.14	0.31	-0.06	0.07	—		

	(0.13)	(0.17)	(0.41)	(0.28)	(0.33)	(0.65)	(0.31)	(0.36)	(0.27)			
11	-0.20 (0.29)	-0.68* (0.32)	-0.79 (0.49)	-0.34 (0.39)	-0.20 (0.29)	-0.39 (0.72)	0.05 (0.41)	-0.32 (0.44)	-0.18 (0.38)	-0.25 (0.32)	—	
12	-0.30 (0.31)	-0.78* (0.33)	-0.89 (0.49)	-0.44 (0.40)	-0.30 (0.43)	-0.49 (0.73)	-0.05 (0.42)	-0.42 (0.45)	-0.28 (0.39)	-0.35 (0.33)	-0.10 (0.42)	—
13	-0.40 (0.38)	-0.88* (0.40)	-0.99 (0.55)	-0.54 (0.46)	-0.41 (0.49)	-0.60 (0.77)	-0.15 (0.48)	-0.52 (0.51)	-0.39 (0.45)	-0.46 (0.40)	-0.20 (0.48)	-0.10 (0.49)
14	0.09 (0.33)	-0.39 (0.35)	-0.50 (0.51)	-0.05 (0.41)	0.09 (0.45)	-0.10 (0.73)	0.34 (0.43)	-0.03 (0.47)	0.11 (0.40)	0.04 (0.32)	0.29 (0.44)	0.39 (0.45)
15	-0.10 (0.29)	-0.58* (0.26)	-0.69 (0.47)	-0.24 (0.37)	-0.11 (0.42)	-0.29 (0.72)	0.15 (0.37)	-0.22 (0.44)	-0.08 (0.37)	-0.16 (0.31)	0.10 (0.41)	0.20 (0.42)
16	0.20 (0.22)	-0.28 (0.22)	-0.39 (0.32)	0.06 (0.32)	0.20 (0.38)	0.01 (0.70)	0.45 (0.34)	0.08 (0.40)	0.22 (0.32)	0.15 (0.25)	0.40 (0.37)	0.50 (0.38)
17	-0.98* (0.26)	-1.46* (0.29)	-1.57* (0.47)	-1.12* (0.36)	-0.99* (0.40)	-1.18 (0.71)	-0.73 (0.39)	-1.10* (0.42)	-0.97* (0.35)	-1.04* (0.29)	-0.79* (0.39)	-0.68 (0.40)
18	-0.27 (0.27)	-0.75* (0.30)	-0.86 (0.48)	-0.42 (0.37)	-0.28 (0.41)	-0.47 (0.72)	-0.02 (0.40)	-0.39 (0.43)	-0.26 (0.36)	-0.33 (0.30)	-0.08 (0.40)	0.03 (0.41)
19	-0.19 (0.30)	-0.67* (0.33)	-0.78 (0.49)	-0.33 (0.40)	-0.20 (0.43)	-0.39 (0.73)	0.06 (0.42)	-0.31 (0.45)	-0.18 (0.38)	-0.25 (0.33)	0.00 (0.42)	0.11 (0.43)
20	-1.71* (0.41)	-2.19* (0.42)	-2.31* (0.56)	-1.86* (0.48)	-1.72* (0.51)	-1.91* (0.78)	-1.46* (0.50)	-1.83* (0.53)	-1.70* (0.47)	-1.77* (0.43)	-1.52* (0.50)	-1.42* (0.51)
21	-1.48* (0.32)	-1.96* (0.35)	-2.07* (0.51)	-1.62* (0.41)	-1.49* (0.44)	-1.68* (0.74)	-1.23* (0.43)	-1.60* (0.47)	-1.47* (0.40)	-1.54* (0.35)	-1.29* (0.44)	-1.18* (0.45)
22	-0.52 (0.27)	-1.00* (0.30)	-1.11 (0.48)	-0.66 (0.37)	-0.53 (0.41)	-0.72 (0.72)	-0.27 (0.40)	-0.64 (0.43)	-0.51 (0.36)	-0.58 (0.30)	-0.32 (0.40)	-0.22 (0.41)
23	0.04 (0.28)	-0.44 (0.31)	-0.55 (0.48)	-0.10 (0.38)	0.03 (0.41)	-0.16 (0.72)	0.29 (0.40)	-0.08 (0.43)	0.05 (0.36)	-0.02 (0.31)	0.24 (0.41)	0.34 (0.41)
24	0.18 (0.36)	-0.30 (0.36)	-0.42 (0.43)	0.03 (0.43)	0.17 (0.47)	-0.02 (0.75)	0.42 (0.44)	0.06 (0.49)	0.19 (0.43)	0.12 (0.38)	0.37 (0.46)	0.47 (0.47)
Treatment	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	0.49 (0.50)	—										
15	0.30 (0.48)	-0.19 (0.44)	—									
16	0.60 (0.44)	0.11 (0.39)	0.30 (0.34)	—								
17	-0.58 (0.46)	-1.08* (0.42)	-0.88* (0.39)	-1.18* (0.34)	—							
18	0.13 (0.47)	-0.37 (0.43)	-0.17 (0.40)	-0.48 (0.35)	0.71 (0.38)	—						
19	0.21 (0.49)	-0.29 (0.45)	-0.09 (0.42)	-0.39 (0.37)	0.79 (0.40)	0.08 (0.41)	—					
20	-1.31* (0.56)	-1.81* (0.52)	-1.62* (0.50)	-1.92* (0.46)	-0.73 (0.48)	-1.44* (0.49)	-1.52* (0.50)	—				
21	-1.08* (0.50)	-1.57* (0.46)	-1.38* (0.43)	-1.68* (0.39)	-0.50 (0.41)	-1.21* (0.42)	-1.29* (0.44)	0.23 (0.52)	—			
22	-0.12 (0.47)	-0.61 (0.42)	-0.42 (0.40)	-0.72* (0.35)	0.46 (0.37)	-0.25 (0.38)	-0.33 (0.40)	1.20* (0.49)	0.96* (0.42)	—		
23	0.44 (0.47)	-0.05 (0.43)	0.14 (0.40)	-0.16 (0.35)	1.02* (0.38)	0.31 (0.39)	0.23 (0.41)	1.76* (0.49)	1.52* (0.42)	0.56 (0.39)	—	
24	0.58 (0.52)	0.08 (0.48)	0.27 (0.44)	-0.03 (0.28)	1.16* (0.44)	0.45 (0.45)	0.37 (0.47)	1.89* (0.54)	1.66* (0.48)	0.69 (0.45)	0.13 (0.46)	—

* Statistically significant

**Legend:

- | | | |
|---|---|----------------------------|
| 1. SRP | 9. SRP + SDD | 17. SRP + SZ gel |
| 2. Control/no treatment | 10. SRP + Doxy | 18. SRP + AV gel |
| 3. Intensive OHI | 11. SRP + AZM | 19. SRP + AZM gel |
| 4. Supragingival cleaning | 12. SRP + MTZ + AMX | 20. SRP + ALN gel |
| 5. Supragingival cleaning + AZM | 13. SRP + Omega 3 + aspirin | 21. SRP + SMV gel |
| 6. Doxy | 14. SRP + aPDT | 22. SRP + CLM gel |
| 7. OHI + SRP | 15. SRP/flap surgery+ Tinidazole + Ampicillin | 23. SRP + TET (topical) |
| 8. SRP + powered subgingival water irrigation | 16. SRP + CHX rinse | 24. SRP + CHX rinse + Doxy |

TABLE 3.28 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

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

**Legend:

- | | | |
|---|---|----------------------------|
| 1. SRP | 9. SRP + SDD | 17. SRP + SZ gel |
| 2. Control/no treatment | 10. SRP + Doxy | 18. SRP + AV gel |
| 3. Intensive OHI | 11. SRP + AZM | 19. SRP + AZM gel |
| 4. Supragingival cleaning | 12. SRP + MTZ + AMX | 20. SRP + ALN gel |
| 5. Supragingival cleaning + AZM | 13. SRP + Omega 3 + aspirin | 21. SRP + SMV gel |
| 6. Doxy | 14. SRP + aPDT | 22. SRP + CLM gel |
| 7. OHI + SRP | 15. SRP/flap surgery+ Tinidazole + Ampicillin | 23. SRP + TET (topical) |
| 8. SRP + powered subgingival water irrigation | 16. SRP + CHX rinse | 24. SRP + CHX rinse + Doxy |

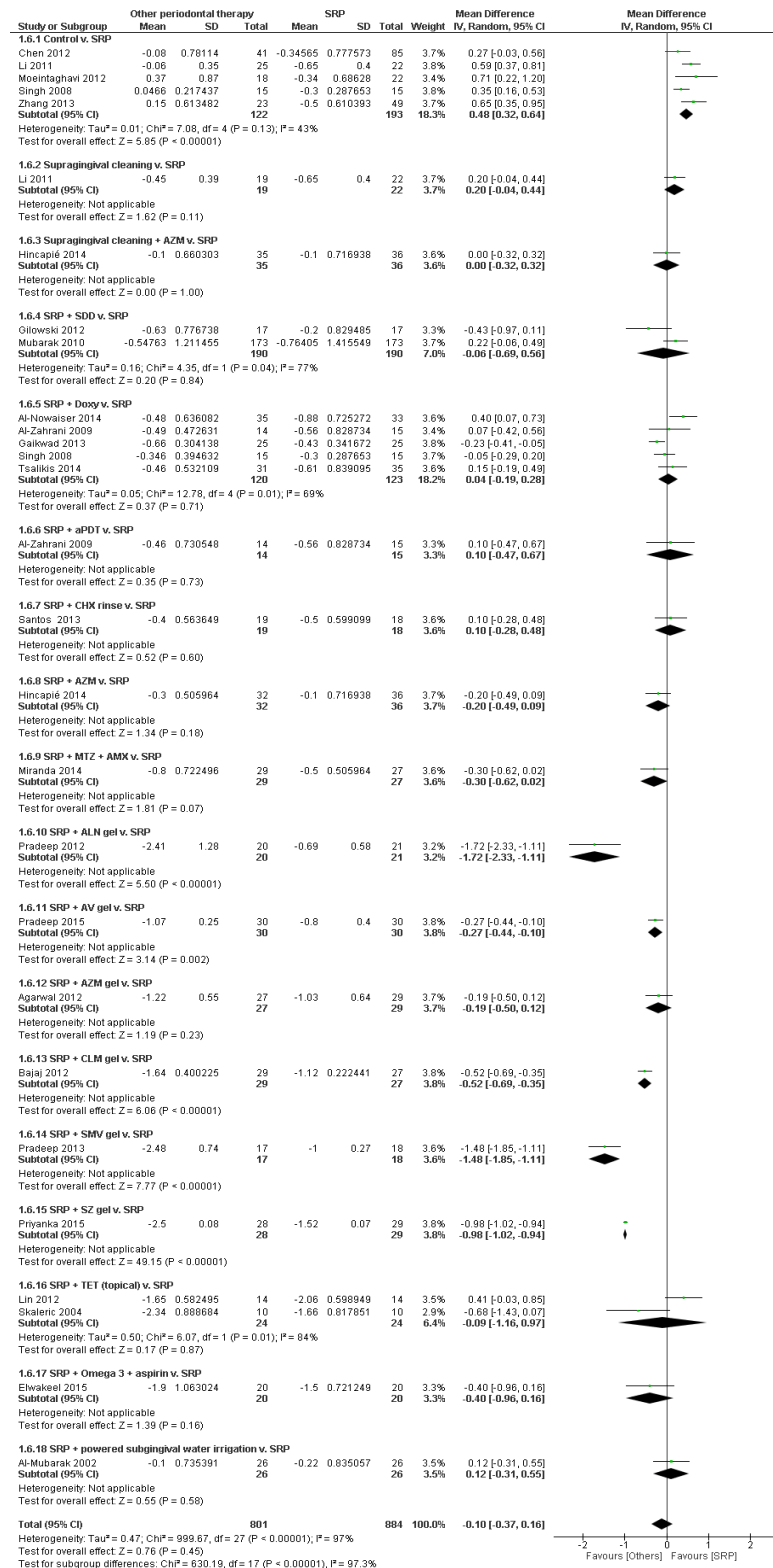
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.29 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR CAL AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	0.48* (0.32 to 0.64)	5	43%	0.48* (0.23 to 0.74)	0.44* (0.34 to 0.55)
Supragingival cleaning	SRP	0.20 (-0.04 to 0.44)	1	NA	0.14 (-0.37 to 0.66)	0.11 (-0.10 to 0.33)
Supragingival cleaning + AZM	SRP	0.00 (-0.32 to 0.32)	1	NA	0.01 (-0.60 to 0.62)	0.00 (-0.32 to 0.32)
SRP + SDD	SRP	-0.06 (-0.69 to 0.56)	2	77%	-0.01 (-0.50 to 0.43)	0.08 (-0.16 to 0.33)
SRP + Doxy	SRP	0.04 (-0.19 to 0.28)	5	69%	0.06 (-0.20 to 0.33)	-0.02 (-0.14 to 0.10)
SRP + aPDT	SRP	0.10 (-0.47 to 0.67)	1	NA	0.09 (-0.54 to 0.75)	0.03 (-0.41 to 0.48)
SRP + CHX rinse	SRP	0.10 (-0.28 to 0.48)	1	NA	0.20 (-0.24 to 0.64)	0.21* (0.01 to 0.41)
SRP + AZM	SRP	-0.20 (-0.49 to 0.09)	1	NA	-0.20 (-0.78 to 0.40)	-0.20 (-0.49 to 0.10)
SRP + MTZ + AMX	SRP	-0.30 (-0.62 to 0.02)	1	NA	-0.30 (-0.91 to 0.31)	-0.30 (-0.62 to 0.03)
SRP + ALN gel	SRP	-1.72* (-2.33 to -1.11)	1	NA	-1.71* (-2.52 to -0.92)	-1.72* (-2.33 to -1.11)
SRP + AV gel	SRP	-0.27* (-0.44 to -0.10)	1	NA	-0.27 (-0.83 to 0.28)	-0.27* (-0.44 to -0.10)
SRP + AZM gel	SRP	-0.19 (-0.50 to 0.12)	1	NA	-0.19 (-0.79 to 0.42)	-0.19 (-0.50 to 0.13)
SRP + CLM gel	SRP	-0.52* (-0.69 to -0.35)	1	NA	-0.52 (-1.06 to 0.03)	-0.52* (-0.69 to -0.35)
SRP + SMV gel	SRP	-1.48* (-1.85 to -1.11)	1	NA	-1.48* (-2.12 to -0.84)	-1.48* (-1.86 to -1.11)
SRP + SZ gel	SRP	-0.98* (-1.02 to -0.94)	1	NA	-0.98* (-1.51 to -0.45)	-0.98* (-1.02 to -0.94)
SRP + TET (topical)	SRP	-0.09 (-1.16 to 0.97)	2	84%	0.04 (-0.52 to 0.57)	0.13 (-0.25 to 0.51)
SRP + Omega 3 + aspirin	SRP	-0.40 (-0.96 to 0.16)	1	NA	-0.40 (-1.15 to 0.36)	-0.40 (-0.96 to 0.17)
SRP + powered subgingival water irrigation	SRP	0.12 (-0.31 to 0.55)	1	NA	0.12 (-0.55 to 0.78)	0.12 (-0.31 to 0.55)
DIC					-51.464	-40.926
Total residual deviance (Unconstrained data points)					65.96 (64 points)	83.95 (64 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.7 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CAL AT 3 MONTHS



SENSITIVITY ANALYSIS

INFLUENCE OF FM-SRP

The network meta-analysis that included only partial mouth SRP had 19 trials, 19 treatments and 1835 patients, providing 23 comparisons based on 17 trials with 2 arms and 2 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.23).

The results showed that compared to control/no treatment, SRP could significantly reduce the CAL. Four treatments had a significantly better effect than SRP (Table 3.30).

TABLE 3.30 CAL---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AMONG TRIALS WITH PMSRP AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.55* (0.14)	—								
3	0.18 (0.24)	-0.37 (0.24)	—							
4	0.2 (0.69)	-0.35 (0.7)	0.02 (0.73)	—						
5	-0.18 (0.28)	-0.73* (0.25)	-0.36 (0.35)	-0.38 (0.74)	—					
6	0.22 (0.28)	-0.33 (0.31)	0.04 (0.37)	0.02 (0.74)	0.4 (0.4)	—				
7	0.06 (0.13)	-0.49* (0.17)	-0.12 (0.27)	-0.14 (0.68)	0.24 (0.3)	-0.16 (0.31)	—			
8	-0.3 (0.3)	-0.84* (0.33)	-0.47 (0.38)	-0.49 (0.75)	-0.11 (0.41)	-0.51 (0.41)	-0.35 (0.32)	—		
9	-0.39 (0.37)	-0.94* (0.4)	-0.57 (0.45)	-0.59 (0.78)	-0.21 (0.47)	-0.61 (0.47)	-0.45 (0.4)	-0.1 (0.47)	—	
10	0.09 (0.32)	-0.46 (0.34)	-0.09 (0.4)	-0.1 (0.74)	0.27 (0.42)	-0.13 (0.42)	0.03 (0.31)	0.39 (0.43)	0.48 (0.49)	—
11	-0.03 (0.29)	-0.58* (0.25)	-0.21 (0.35)	-0.23 (0.74)	0.15 (0.35)	-0.25 (0.4)	-0.09 (0.3)	0.26 (0.41)	0.36 (0.47)	-0.13 (0.42)
12	0.35 (0.3)	-0.2 (0.26)	0.17 (0.36)	0.15 (0.74)	0.53 (0.36)	0.13 (0.41)	0.29 (0.32)	0.65 (0.42)	0.74 (0.48)	0.26 (0.43)
13	-0.98* (0.24)	-1.53* (0.28)	-1.16* (0.35)	-1.18 (0.73)	-0.8* (0.37)	-1.2* (0.37)	-1.04* (0.28)	-0.68 (0.38)	-0.59 (0.45)	-1.07* (0.4)
14	-0.27 (0.26)	-0.82* (0.29)	-0.45 (0.35)	-0.47 (0.74)	-0.09 (0.38)	-0.49 (0.38)	-0.33 (0.29)	0.02 (0.39)	0.12 (0.45)	-0.36 (0.41)
15	-0.19 (0.29)	-0.73* (0.32)	-0.37 (0.38)	-0.38 (0.74)	-0.01 (0.4)	-0.4 (0.4)	-0.25 (0.31)	0.11 (0.41)	0.21 (0.47)	-0.28 (0.43)
16	-1.71* (0.4)	-2.26* (0.42)	-1.89* (0.46)	-1.91* (0.79)	-1.53* (0.49)	-1.93* (0.48)	-1.77* (0.42)	-1.42* (0.49)	-1.32* (0.55)	-1.81* (0.51)
17	-1.48* (0.31)	-2.03* (0.34)	-1.66* (0.39)	-1.68* (0.75)	-1.3* (0.42)	-1.7* (0.42)	-1.54* (0.33)	-1.19* (0.43)	-1.09* (0.49)	-1.57* (0.44)
18	-0.52* (0.26)	-1.07* (0.29)	-0.7 (0.35)	-0.72 (0.73)	-0.34 (0.38)	-0.74 (0.38)	-0.58* (0.28)	-0.22 (0.39)	-0.13 (0.45)	-0.61 (0.41)
19	0.41	-0.13	0.24	0.22	0.59	0.2	0.35	0.71	0.81	0.32

	(0.33)	(0.36)	(0.41)	(0.76)	(0.44)	(0.43)	(0.35)	(0.44)	(0.5)	(0.46)
20	0.32 (0.4)	-0.22 (0.38)	0.14 (0.45)	0.13 (0.79)	0.5 (0.45)	0.11 (0.49)	0.26 (0.42)	0.62 (0.5)	0.72 (0.55)	0.23 (0.51)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.38 (0.36)	—								
13	-0.95* (0.38)	-1.33* (0.38)	—							
14	-0.24 (0.39)	-0.62 (0.39)	0.71 (0.35)	—						
15	-0.15 (0.4)	-0.54 (0.41)	0.79* (0.38)	0.08 (0.38)	—					
16	-1.68* (0.49)	-2.06* (0.5)	-0.73 (0.46)	-1.44* (0.47)	-1.53* (0.49)	—				
17	-1.45* (0.42)	-1.83* (0.43)	-0.5 (0.39)	-1.21* (0.4)	-1.29* (0.42)	0.23 (0.5)	—			
18	-0.49 (0.38)	-0.87* (0.39)	0.46 (0.35)	-0.25 (0.36)	-0.33 (0.38)	1.19* (0.47)	0.96* (0.4)	—		
19	0.45 (0.44)	0.06 (0.44)	1.39* (0.41)	0.69 (0.42)	0.6 (0.44)	2.13* (0.52)	1.9* (0.45)	0.93* (0.42)	—	
20	0.36 (0.45)	-0.03 (0.27)	1.3* (0.47)	0.59 (0.48)	0.51 (0.49)	2.04* (0.56)	1.8* (0.51)	0.84 (0.48)	-0.09 (0.52)	—

* Statistically significant

**Legend:

- | | |
|----------------------------|---|
| 1. SRP | 11. SRP/flap surgery+ Tinidazole + Ampicillin |
| 2. Control/no treatment | 12. SRP + CHX rinse |
| 3. Supragingival cleaning | 13. SRP + SZ gel |
| 4. Doxy | 14. SRP + AV gel |
| 5. OHI + SRP | 15. SRP + AZM gel |
| 6. SRP + SDD | 16. SRP + ALN gel |
| 7. SRP + Doxy | 17. SRP + SMV gel |
| 8. SRP + MTZ + AMX | 18. SRP + CLM gel |
| 9. SRP + Omega 3 + aspirin | 19. SRP + TET (topical) |
| 10. SRP + aPDT | 20. SRP + CHX rinse + Doxy |

End of study

Out of the 40 trials that have reported the outcome of CAL, 5 were not included in this network meta-analysis. Two of them compared FMSRP with PMSRP (Santos 2012; Santos 2009) and the other one (Mendonca 2012/Bezerra 2014; Llambés 2012/2008/2005; Raman 2014) was not connected to the network.

This network meta-analysis included 31 therapies and 50 comparisons giving 29 two-arm trials, 5 three-arm trials and 1 four-arm trial. There was no evidence of inconsistency in the network (Figure A8.25).

Compared to control/no treatment, SRP had a significant effect on improving CAL. Ten therapies had better effects than SRP (Table 3.31-3.32). Direct evidence (Figure 3.8) was not always consistent with the mixed estimates. Direct comparisons showed that SRP was better than supragingival cleaning; however, the difference was no longer significant when indirect evidence was incorporated. Both direct evidence and estimates from fixed-

effects model suggested “SRP plus systemic ALN” and “SRP plus systemic Omega 3 and aspirin” had better effect than SRP; however, the differences were not conserved in random-effects model. Based on DIC and total residual deviance, random-effect model seems to be a better fit of the data (Table 3.33).

TABLE 3.31 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.59* (0.11)	—									
3	0.23 (0.19)	-0.36 (0.19)	—								
4	0.10 (0.27)	-0.48 (0.29)	-0.13 (0.33)	—							
5	0.19 (0.66)	-0.40 (0.67)	-0.04 (0.68)	0.09 (0.71)	—						
6	0.12 (0.30)	-0.46 (0.32)	-0.11 (0.35)	0.02 (0.40)	-0.07 (0.72)	—					
7	-0.50* (0.15)	-1.08* (0.18)	-0.73* (0.24)	-0.60 (0.31)	-0.69 (0.68)	-0.62 (0.34)	—				
8	0.04 (0.11)	-0.55* (0.15)	-0.19 (0.21)	-0.06 (0.29)	-0.15 (0.65)	-0.08 (0.32)	0.54* (0.19)	—			
9	0.10 (0.26)	-0.48 (0.28)	-0.13 (0.32)	0.00 (0.25)	-0.09 (0.71)	-0.02 (0.39)	0.60 (0.30)	0.06 (0.28)	—		
10	-0.52 (0.29)	-1.11* (0.32)	-0.75* (0.35)	-0.62 (0.40)	-0.71 (0.73)	-0.64 (0.42)	-0.02 (0.33)	-0.56 (0.31)	-0.62 (0.39)	—	
11	-0.65 (0.37)	-1.23* (0.39)	-0.88* (0.41)	-0.75 (0.46)	-0.84 (0.75)	-0.77 (0.48)	-0.15 (0.40)	-0.69 (0.39)	-0.75 (0.45)	-0.13 (0.47)	—
12	0.08 (0.29)	-0.51 (0.31)	-0.15 (0.35)	-0.02 (0.40)	-0.11 (0.71)	-0.04 (0.42)	0.58 (0.33)	0.04 (0.29)	-0.02 (0.39)	0.60 (0.41)	0.73 (0.47)
13	-0.01 (0.19)	-0.59* (0.18)	-0.23 (0.25)	-0.11 (0.33)	-0.19 (0.68)	-0.13 (0.35)	0.49* (0.22)	-0.04 (0.21)	-0.11 (0.32)	0.52 (0.35)	0.64 (0.41)
14	0.06 (0.26)	-0.53* (0.24)	-0.17 (0.31)	-0.04 (0.37)	-0.13 (0.70)	-0.06 (0.39)	0.56 (0.29)	0.02 (0.28)	-0.04 (0.37)	0.58 (0.39)	0.71 (0.45)
15	-0.19 (0.24)	-0.78* (0.21)	-0.42 (0.28)	-0.30 (0.36)	-0.38 (0.70)	-0.31 (0.38)	0.30 (0.28)	-0.23 (0.26)	-0.29 (0.35)	0.33 (0.38)	0.45 (0.44)
16	-0.84* (0.24)	-1.43* (0.25)	-1.07* (0.30)	-0.94* (0.36)	-1.03 (0.70)	-0.96* (0.39)	-0.34 (0.25)	-0.88* (0.26)	-0.94* (0.35)	-0.32 (0.38)	-0.19 (0.44)
17	-0.40 (0.44)	-0.99* (0.44)	-0.63 (0.47)	-0.50 (0.52)	-0.59 (0.79)	-0.52 (0.53)	0.10 (0.45)	-0.44 (0.45)	-0.50 (0.51)	0.12 (0.53)	0.25 (0.57)
18	-0.01 (0.40)	-0.59 (0.40)	-0.24 (0.44)	-0.11 (0.48)	-0.20 (0.77)	-0.13 (0.50)	0.49 (0.42)	-0.05 (0.41)	-0.11 (0.48)	0.51 (0.50)	0.64 (0.54)
19	-0.41 (0.32)	-0.99* (0.32)	-0.64 (0.37)	-0.51 (0.42)	-0.60 (0.73)	-0.53 (0.44)	0.09 (0.34)	-0.44 (0.34)	-0.51 (0.41)	0.12 (0.44)	0.24 (0.49)
20	-0.48 (0.52)	-1.07* (0.52)	-0.71 (0.55)	-0.58 (0.59)	-0.67 (0.84)	-0.60 (0.60)	0.02 (0.53)	-0.52 (0.53)	-0.58 (0.59)	0.04 (0.60)	0.17 (0.64)
21	0.00 (0.24)	-0.58* (0.21)	-0.23 (0.29)	-0.10 (0.36)	-0.19 (0.70)	-0.12 (0.38)	0.50 (0.28)	-0.03 (0.26)	-0.10 (0.35)	0.53 (0.38)	0.65 (0.44)
22	-2.83* (0.40)	-3.42* (0.42)	-3.06* (0.44)	-2.94* (0.48)	-3.02* (0.77)	-2.96* (0.50)	-2.34* (0.43)	-2.87* (0.42)	-2.94* (0.48)	-2.31* (0.50)	-2.19* (0.54)
23	-0.83* (0.22)	-1.41* (0.25)	-1.06* (0.29)	-0.93* (0.35)	-1.02 (0.70)	-0.95* (0.37)	-0.33 (0.27)	-0.87* (0.25)	-0.93* (0.34)	-0.31 (0.37)	-0.18 (0.43)
24	-2.28* (0.21)	-2.87* (0.23)	-2.51* (0.28)	-2.38* (0.34)	-2.47* (0.69)	-2.40* (0.36)	-1.78* (0.26)	-2.32* (0.23)	-2.38* (0.33)	-1.76* (0.36)	-1.63* (0.42)
25	-0.60* (0.23)	-1.19* (0.26)	-0.83* (0.30)	-0.70 (0.35)	-0.79 (0.70)	-0.72 (0.38)	-0.10 (0.28)	-0.64* (0.26)	-0.70* (0.34)	-0.08 (0.38)	0.05 (0.44)

26	-0.60* (0.24)	-1.19* (0.26)	-0.83* (0.30)	-0.70 (0.36)	-0.79 (0.70)	-0.72 (0.38)	-0.10 (0.28)	-0.64* (0.26)	-0.70* (0.35)	-0.08 (0.38)	0.05 (0.44)
27	-1.98* (0.37)	-2.57* (0.39)	-2.21* (0.42)	-2.09* (0.46)	-2.17* (0.76)	-2.10* (0.47)	-1.49* (0.40)	-2.02* (0.39)	-2.08* (0.45)	-1.46* (0.47)	-1.34* (0.53)
28	-0.17 (0.29)	-0.76* (0.31)	-0.40 (0.35)	-0.27 (0.39)	-0.36 (0.72)	-0.29 (0.42)	0.33 (0.33)	-0.21 (0.31)	-0.27 (0.39)	0.35 (0.41)	0.48 (0.47)
29	-1.10* (0.50)	-1.69* (0.49)	-1.33* (0.52)	-1.20* (0.57)	-1.29 (0.82)	-1.22* (0.58)	-0.60 (0.51)	-1.14* (0.51)	-1.20* (0.56)	-0.58 (0.58)	-0.45 (0.62)
30	0.39 (0.21)	-0.20 (0.19)	0.16 (0.27)	0.29 (0.34)	0.20 (0.69)	0.27 (0.36)	0.89* (0.25)	0.35 (0.23)	0.29 (0.33)	0.91* (0.36)	1.04* (0.42)
31	-2.31* (0.49)	-2.90* (0.48)	-2.54* (0.52)	-2.41* (0.56)	-2.50* (0.81)	-2.43* (0.57)	-1.81* (0.50)	-2.35* (0.50)	-2.41* (0.55)	-1.79* (0.57)	-1.66* (0.61)
Treatment	12	13	14	15	16	17	18	19	20	21	22
12	—										
13	-0.09 (0.35)	—									
14	-0.02 (0.39)	0.06 (0.25)	—								
15	-0.27 (0.38)	-0.19 (0.27)	-0.25 (0.32)	—							
16	-0.92* (0.38)	-0.84* (0.26)	-0.90* (0.33)	-0.65 (0.33)	—						
17	-0.48 (0.53)	-0.40 (0.40)	-0.46 (0.47)	-0.21 (0.48)	0.44 (0.47)	—					
18	-0.09 (0.50)	0.00 (0.36)	-0.07 (0.43)	0.18 (0.45)	0.83 (0.44)	0.39 (0.53)	—				
19	-0.49 (0.44)	-0.40 (0.26)	-0.46 (0.36)	-0.21 (0.38)	0.44 (0.37)	-0.01 (0.48)	-0.40 (0.44)	—			
20	-0.56 (0.60)	-0.48 (0.49)	-0.54 (0.54)	-0.29 (0.56)	0.36 (0.55)	-0.08 (0.28)	-0.47 (0.61)	-0.08 (0.55)	—		
21	-0.08 (0.38)	0.01 (0.28)	-0.05 (0.32)	0.20 (0.30)	0.85* (0.33)	0.41 (0.48)	0.01 (0.45)	0.41 (0.38)	0.49 (0.56)	—	
22	-2.92* (0.50)	-2.83* (0.44)	-2.89* (0.48)	-2.64* (0.47)	-1.99* (0.47)	-2.43* (0.59)	-2.83* (0.57)	-2.43* (0.51)	-2.35* (0.65)	-2.84* (0.47)	—
23	-0.91* (0.37)	-0.82* (0.29)	-0.89* (0.34)	-0.63 (0.33)	0.01 (0.33)	-0.43 (0.49)	-0.82 (0.46)	-0.42 (0.39)	-0.35 (0.57)	-0.83* (0.33)	2.01* (0.46)
24	-2.36* (0.36)	-2.28* (0.28)	-2.34* (0.33)	-2.09* (0.31)	-1.44* (0.32)	-1.88* (0.48)	-2.27* (0.45)	-1.87* (0.38)	-1.80* (0.56)	-2.29* (0.32)	0.55 (0.45)
25	-0.68 (0.37)	-0.59 (0.30)	-0.66 (0.35)	-0.41 (0.33)	0.24 (0.33)	-0.20 (0.49)	-0.59 (0.46)	-0.19 (0.40)	-0.12 (0.57)	-0.60 (0.33)	2.24* (0.46)
26	-0.68 (0.38)	-0.60 (0.30)	-0.66 (0.36)	-0.41 (0.34)	0.24 (0.34)	-0.20 (0.50)	-0.59 (0.47)	-0.19 (0.40)	-0.12 (0.58)	-0.61 (0.34)	2.23* (0.47)
27	-2.06* (0.47)	-1.98* (0.42)	-2.04* (0.45)	-1.79* (0.44)	-1.14* (0.44)	-1.58* (0.58)	-1.97* (0.55)	-1.58* (0.50)	-1.50* (0.64)	-1.99* (0.44)	0.85 (0.55)
28	-0.25 (0.41)	-0.17 (0.34)	-0.23 (0.39)	0.02 (0.37)	0.67 (0.37)	0.23 (0.53)	-0.16 (0.49)	0.23 (0.44)	0.31 (0.60)	-0.18 (0.38)	2.66* (0.49)
29	-1.18* (0.58)	-1.10* (0.49)	-1.16* (0.43)	-0.91 (0.53)	-0.26 (0.54)	-0.70 (0.64)	-1.09 (0.61)	-0.70 (0.56)	-0.62 (0.70)	-1.11* (0.54)	1.73* (0.64)
30	0.31 (0.36)	0.40 (0.20)	0.33 (0.29)	0.58* (0.28)	1.23* (0.29)	0.79 (0.44)	0.40 (0.41)	0.80* (0.33)	0.87 (0.53)	0.39 (0.28)	3.23* (0.45)
31	-2.39* (0.57)	-2.31* (0.45)	-2.37* (0.51)	-2.12* (0.53)	-1.47* (0.52)	-1.91* (0.60)	-2.30* (0.57)	-1.90* (0.52)	-1.83* (0.66)	-2.32* (0.53)	0.52 (0.63)
Treatment	23	24	25	26	27	28	29	30	31		
23	—										
24	-1.45* (0.30)	—									
25	0.23 (0.32)	1.68* (0.31)	—								
26	0.23 (0.33)	1.68* (0.32)	0.00 (0.33)	—							
27	-1.16* (0.43)	0.30 (0.43)	-1.38* (0.44)	-1.38* (0.44)	—						
28	0.65	2.11*	0.43	0.43	1.81*	—					

	(0.37)	(0.35)	(0.37)	(0.38)	(0.47)						
29	-0.27 (0.55)	1.18* (0.54)	-0.50 (0.55)	-0.50 (0.55)	0.88 (0.62)	-0.93 (0.58)	—				
30	1.22* (0.30)	2.67* (0.29)	0.99* (0.31)	0.99* (0.32)	2.37* (0.43)	0.56 (0.36)	1.49* (0.52)	—			
31	-1.48* (0.54)	-0.03 (0.53)	-1.71* (0.54)	-1.71* (0.54)	-0.33 (0.62)	-2.14* (0.56)	-1.21 (0.67)	-2.70* (0.49)	—		

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 17. SRP + Doxy+ intensive maintenance |
| 2. Control/no treatment | 18. SRP + AMX+ intensive maintenance |
| 3. Supragingival cleaning | 19. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning + AZM | 20. SRP+ Doxy+ aPDT + intensive maintenance |
| 5. Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 7. SRP + SDD | 23. SRP + CLM gel |
| 8. SRP + Doxy | 24. SRP + SZ gel |
| 9. SRP + AZM | 25. SRP + AV gel |
| 10. SRP + ALN | 26. SRP + AZM gel |
| 11. SRP + Omega 3 + aspirin | 27. SRP + ALN gel |
| 12. SRP + aPDT | 28. SRP + TET (topical) |
| 13. SRP + intensive maintenance | 29. SRP + TET (topical) + non-intensive maintenance |
| 14. SRP + non-intensive maintenance | 30. SRP + CHX rinse + intensive maintenance |
| 15. OHI+ SRP+ intensive maintenance | 31. SRP + Doxy gel+ intensive maintenance |
| 16. SRP + SDD + intensive maintenance | |

**TABLE 3.32 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

T**	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	26	27	28	29	30	31
1																															
2																															
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T: treatment

**Legend:

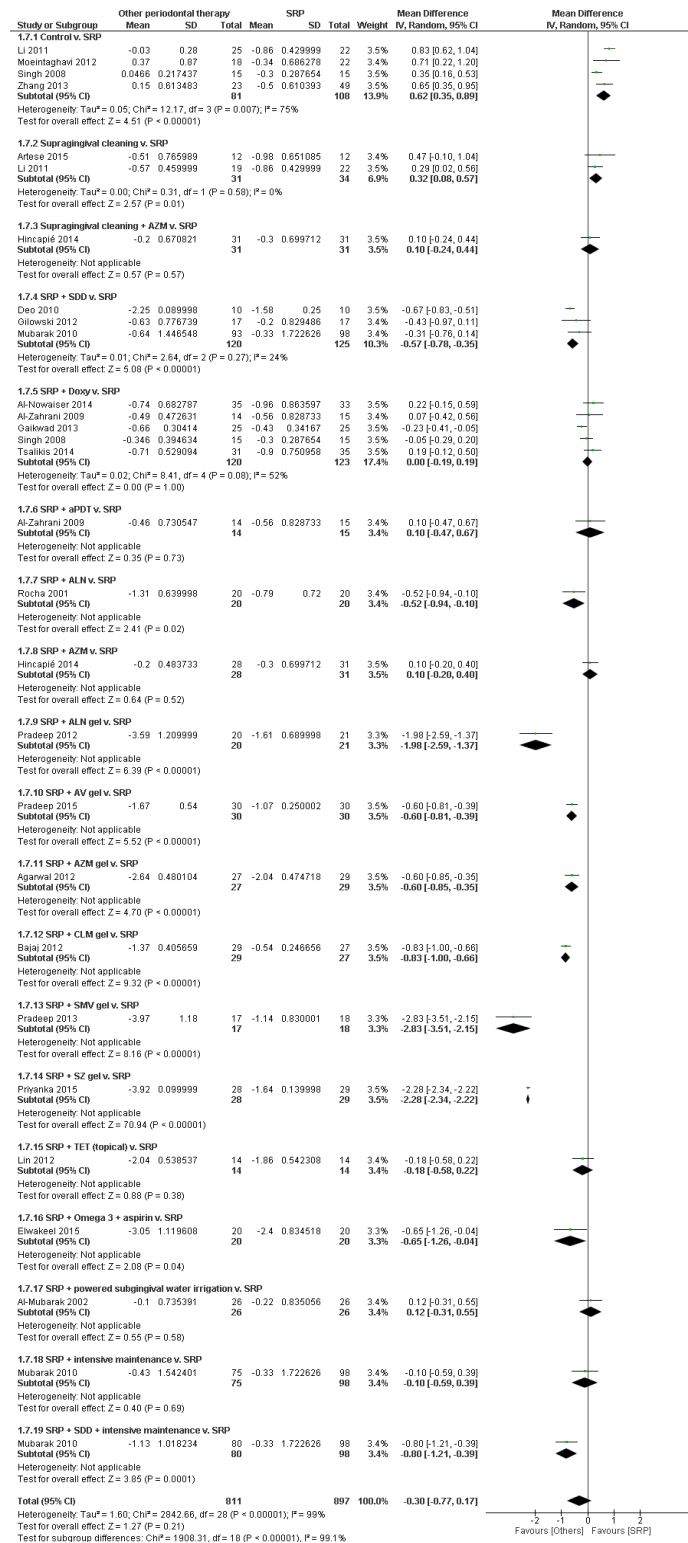
- | | |
|---|---|
| 1. SRP | 17. SRP + Doxy+ intensive maintenance |
| 2. Control/no treatment | 18. SRP + AMX+ intensive maintenance |
| 3. Supragingival cleaning | 19. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning + AZM | 20. SRP+ Doxy+ aPDT + intensive maintenance |
| 5. Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 7. SRP + SDD | 23. SRP + CLM gel |
| 8. SRP + Doxy | 24. SRP + SZ gel |
| 9. SRP + AZM | 25. SRP + AV gel |
| 10. SRP + ALN | 26. SRP + AZM gel |
| 11. SRP + Omega 3 + aspirin | 27. SRP + ALN gel |
| 12. SRP + aPDT | 28. SRP + TET (topical) |
| 13. SRP + intensive maintenance | 29. SRP + TET (topical) + non-intensive maintenance |
| 14. SRP + non-intensive maintenance | 30. SRP + CHX rinse + intensive maintenance |
| 15. OHI+ SRP+ intensive maintenance | 31. SRP + Doxy gel+ intensive maintenance |
| 16. SRP + SDD + intensive maintenance | |

Green cells indicate a statistically significant improvement of HbA1c; 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 3.33 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR CAL AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	0.62* (0.35 to 0.89)	4	75%	0.59* (0.36 to 0.81)	0.55* (0.44 to 0.66)
Supragingival cleaning	SRP	0.32* (0.08 to 0.57)	2	0%	0.23 (-0.13 to 0.61)	0.14 (-0.08 to 0.36)
Supragingival cleaning + AZM	SRP	0.10 (-0.24 to 0.44)	1	NA	0.10 (-0.43 to 0.63)	0.10 (-0.24 to 0.44)
SRP + SDD	SRP	-0.57* (-0.78 to -0.35)	3	24%	-0.50* (-0.79 to -0.18)	-0.59* (-0.74 to -0.45)
SRP + Doxy	SRP	0.00 (-0.19 to 0.19)	5	52%	0.04 (-0.18 to 0.27)	-0.02 (-0.14 to 0.10)
SRP + aPDT	SRP	0.10 (-0.47 to 0.67)	1	NA	0.08 (-0.49 to 0.66)	0.03 (-0.41 to 0.48)
SRP + ALN	SRP	-0.52* (-0.94 to -0.10)	1	NA	-0.52 (-1.10 to 0.06)	-0.52* (-0.94 to -0.10)
SRP + AZM	SRP	0.10 (-0.20 to 0.40)	1	NA	0.10 (-0.40 to 0.61)	0.10 (-0.20 to 0.41)
SRP + ALN gel	SRP	-1.98* (-2.59 to -1.37)	1	NA	-1.98* (-2.72 to -1.25)	-1.98* (-2.59 to -1.37)
SRP + AV gel	SRP	-0.60* (-0.81 to -0.39)	1	NA	-0.60* (-1.06 to -0.14)	-0.60* (-0.81 to -0.39)
SRP + AZM gel	SRP	-0.60* (-0.85 to -0.35)	1	NA	-0.60* (-1.08 to -0.13)	-0.60* (-0.85 to -0.35)
SRP + CLM gel	SRP	-0.83* (-1.00 to -0.66)	1	NA	-0.83* (-1.28 to -0.38)	-0.83* (-1.01 to -0.66)
SRP + SMV gel	SRP	-2.83* (-3.51 to -2.15)	1	NA	-2.83* (-3.61 to -2.04)	-2.83* (-3.51 to -2.15)
SRP + SZ gel	SRP	-2.28* (-2.34 to -2.22)	1	NA	-2.28* (-2.70 to -1.86)	-2.28* (-2.34 to -2.22)
SRP + TET (topical)	SRP	-0.18 (-0.58 to 0.22)	1	NA	-0.17 (-0.74 to 0.39)	-0.18 (-0.58 to 0.22)
SRP + Omega 3 + aspirin	SRP	-0.65* (-1.26 to -0.04)	1	NA	-0.65 (-1.38 to 0.08)	-0.65* (-1.26 to -0.04)
SRP + powered subgingival water irrigation	SRP	0.12 (-0.31 to 0.55)	1	NA	0.12 (-0.47 to 0.71)	0.12 (-0.31 to 0.55)
SRP + intensive maintenance	SRP	-0.10 (-0.59 to 0.39)	1	NA	-0.01 (-0.38 to 0.36)	-0.03 (-0.27 to 0.21)
SRP + SDD + intensive maintenance	SRP	-0.80* (-1.21 to -0.39)	1	NA	-0.84* (-1.31 to -0.36)	-0.90* (-1.20 to -0.59)
DIC					-43.077	-31.227
Total residual deviance (Unconstrained data points)					74.94 (77 points)	93.43 (77 points)
Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.						

FIGURE 3.8 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CAL AT END OF STUDY



3.2.5 BLEEDING ON PROBING (BOP)

3 months

Thirty-four trials reported BOP as an outcome. The trials that informed the evidence network for BOP at 3 months included 26 trials, 24 treatment and 2308 participants, providing 32 comparisons. Eight trials were not included in this network meta-analysis. Three of them did not provide data at 3 month (Koromantzios 2011/2012/2014; Rocha 2001; Artese 2015); 2 trials compared FMSRP with PMSRP (Santos 2012; Santos 2009) and 3 trials were not connected to the network (Macedo 2014; O'Connell 2008; Rodrigues 2003). There was no evidence of inconsistency in the network (Figure A8.27).

Results showed that, compared to control/no treatment, SRP had a significant effect on improving (lowering) BOP. “SRP plus EO-based rinse” showed a significantly better effect than SRP. There was no statistically significant difference between SRP and other periodontal therapies (Table 3.34-3.35).

TABLE 3.34 BOP ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	1.54* (0.54)	—										
3	0.95 (1.28)	-0.59 (1.28)	—									
4	0.42 (0.92)	-1.12 (0.92)	-0.53 (1.54)	—								
5	-0.20 (1.00)	-1.74 (1.14)	-1.15 (1.63)	-0.62 (1.37)	—							
6	0.78 (1.17)	-0.76 (1.29)	-0.17 (1.74)	0.36 (1.49)	0.98 (1.54)	—						
7	-1.79 (1.16)	-3.33* (1.03)	-2.74 (1.65)	-2.21 (1.39)	-1.59 (1.54)	-2.57 (1.66)	—					
8	-0.52 (0.71)	-2.06* (0.89)	-1.47 (1.46)	-0.94 (1.17)	-0.32 (1.24)	-1.30 (1.37)	1.27 (1.36)	—				
9	-0.10 (0.59)	-1.63* (0.80)	-1.04 (1.42)	-0.51 (1.10)	0.11 (1.17)	-0.87 (1.01)	1.70 (1.31)	0.42 (0.92)	—			
10	-0.71 (1.00)	-2.24 (1.14)	-1.66 (1.63)	-1.13 (1.36)	-0.51 (1.00)	-1.49 (1.54)	1.08 (1.54)	-0.19 (1.24)	-0.61 (1.16)	—		
11	-1.28 (1.01)	-2.82* (1.13)	-2.23 (1.63)	-1.70 (1.36)	-1.08 (1.43)	-2.06 (1.54)	0.51 (1.52)	-0.76 (1.23)	-1.19 (1.16)	-0.57 (1.43)	—	
12	-0.30 (1.00)	-1.83 (1.13)	-1.24 (1.62)	-0.72 (1.36)	-0.10 (1.42)	-1.08 (1.55)	1.49 (1.53)	0.22 (1.23)	-0.20 (1.16)	0.41 (1.42)	0.98 (1.42)	—
13	0.36 (0.95)	-1.17 (1.09)	-0.58 (1.61)	-0.06 (1.33)	0.56 (1.39)	-0.41 (1.39)	2.15 (1.50)	0.88 (1.18)	0.46 (0.95)	1.07 (1.38)	1.65 (1.38)	0.66 (1.38)
14	-0.63	-2.17*	-1.58	-1.05	-0.43	-1.41	1.16	-0.11	-0.54	0.08	0.65	-0.33

	(1.13)	(1.00)	(1.63)	(1.36)	(1.51)	(1.64)	(1.43)	(1.34)	(1.28)	(1.51)	(1.51)	(1.52)
15	0.52 (0.75)	-1.02 (0.75)	-0.43 (1.03)	0.10 (1.12)	0.72 (1.26)	-0.26 (1.40)	2.31 (1.28)	1.04 (1.03)	0.61 (0.96)	1.23 (1.26)	1.80 (1.26)	0.81 (1.25)
16	-1.01 (1.01)	-2.55* (1.15)	-1.96 (1.63)	-1.43 (1.36)	-0.81 (1.42)	-1.79 (1.55)	0.78 (1.55)	-0.49 (1.24)	-0.92 (1.17)	-0.30 (1.43)	0.27 (1.43)	-0.71 (1.43)
17	-0.66 (1.01)	-2.19 (1.13)	-1.60 (1.62)	-1.07 (1.36)	-0.45 (1.42)	-1.43 (1.55)	1.14 (1.55)	-0.14 (1.23)	-0.56 (1.17)	0.05 (1.43)	0.63 (1.42)	-0.36 (1.42)
18	-0.84 (1.03)	-2.37* (1.16)	-1.79 (1.64)	-1.26 (1.39)	-0.64 (1.43)	-1.62 (1.55)	0.95 (1.55)	-0.32 (1.25)	-0.74 (1.19)	-0.13 (1.44)	0.44 (1.44)	-0.54 (1.44)
19	-1.33 (1.04)	-2.87* (1.17)	-2.28 (1.64)	-1.75 (1.39)	-1.13 (1.44)	-2.11 (1.55)	0.46 (1.55)	-0.81 (1.27)	-1.24 (1.19)	-0.62 (1.45)	-0.05 (1.44)	-1.03 (1.45)
20	-0.95 (1.01)	-2.48* (1.14)	-1.89 (1.63)	-1.37 (1.37)	-0.75 (1.43)	-1.72 (1.54)	0.84 (1.53)	-0.43 (1.24)	-0.85 (1.17)	-0.24 (1.42)	0.34 (1.43)	-0.65 (1.43)
21	-3.32* (1.05)	-4.86* (1.17)	-4.27* (1.65)	-3.74* (1.39)	-3.12* (1.45)	-4.10* (1.58)	-1.53 (1.56)	-2.80* (1.27)	-3.23* (1.20)	-2.62 (1.44)	-2.04 (1.45)	-3.03* (1.45)
22	-1.27 (1.06)	-2.81* (1.19)	-2.22 (1.66)	-1.69 (1.40)	-1.07 (1.46)	-2.05 (1.58)	0.52 (1.57)	-0.75 (1.28)	-1.18 (1.22)	-0.56 (1.45)	0.01 (1.47)	-0.97 (1.45)
23	0.18 (1.16)	-1.36 (1.03)	-0.77 (1.65)	-0.24 (1.39)	0.38 (1.55)	-0.60 (1.65)	1.97 (1.45)	0.70 (1.36)	0.27 (1.30)	0.89 (1.54)	1.46 (1.54)	0.48 (1.53)
24	0.05 (1.25)	-1.49 (1.25)	-0.90 (1.44)	-0.37 (1.50)	0.25 (1.61)	-0.73 (1.73)	1.84 (1.62)	0.57 (1.44)	0.14 (1.39)	0.76 (1.60)	1.33 (1.60)	0.35 (1.60)
Treatment	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	-0.99 (1.49)	—										
15	0.15 (1.22)	1.15 (1.25)	—									
16	-1.38 (1.39)	-0.38 (1.53)	-1.53 (1.26)	—								
17	-1.02 (1.39)	-0.02 (1.51)	-1.17 (1.25)	0.36 (1.44)	—							
18	-1.20 (1.40)	-0.21 (1.53)	-1.36 (1.27)	0.17 (1.46)	-0.18 (1.45)	—						
19	-1.69 (1.40)	-0.70 (1.53)	-1.85 (1.27)	-0.32 (1.45)	-0.67 (1.45)	-0.49 (1.47)	—					
20	-1.31 (1.38)	-0.32 (1.51)	-1.46 (1.25)	0.07 (1.42)	-0.29 (1.42)	-0.11 (1.44)	0.38 (1.45)	—				
21	-3.69* (1.41)	-2.69 (1.54)	-3.84* (1.28)	-2.31 (1.46)	-2.67 (1.45)	-2.49 (1.47)	-1.99 (1.48)	-2.38 (1.46)	—			
22	-1.63 (1.44)	-0.64 (1.55)	-1.79 (1.30)	-0.26 (1.48)	-0.61 (1.47)	-0.43 (1.48)	0.06 (1.49)	-0.32 (1.46)	2.05 (1.50)	—		
23	-0.19 (1.50)	0.81 (1.43)	-0.34 (1.28)	1.19 (1.55)	0.83 (1.54)	1.02 (1.54)	1.51 (1.56)	1.13 (1.53)	3.50* (1.56)	1.45 (1.57)	—	
24	-0.32 (1.59)	0.68 (1.60)	-0.47 (1.00)	1.06 (1.61)	0.70 (1.60)	0.89 (1.61)	1.38 (1.63)	0.99 (1.61)	3.37* (1.63)	1.32 (1.64)	-0.13 (1.62)	—

* Statistically significant

**Legend:

- | | |
|--|---|
| 1. SRP | 13. SRP + aPDT |
| 2. Control/no treatment | 14. SRP/flap surgery+ Tinidazole + Ampicillin |
| 3. Intensive OHI | 15. SRP + CHX rinse |
| 4. Supragingival cleaning | 16. SRP + AV gel |
| 5. Supragingival cleaning + AZM | 17. SRP + AZM gel |
| 6. Doxy | 18. SRP + ALN gel |
| 7. OHI + SRP | 19. SRP + SMV gel |
| 8. SRP + SDD | 20. SRP + CLM gel |
| 9. SRP + Doxy | 21. SRP + EO-based rinse |
| 10. SRP + AZM | 22. SRP + TET (topical) |
| 11. SRP + MTZ + AMX | 23. SRP + TET (topical) + intensive maintenance |
| 12. SRP + powered subgingival water irrigation | 24. SRP + CHX rinse + Doxy |

TABLE 3.35 BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

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

**Legend:

- | | |
|--|---|
| 1. SRP | 13. SRP + aPDT |
| 2. Control/no treatment | 14. SRP/flap surgery+ Tinidazole + Ampicillin |
| 3. Intensive OHI | 15. SRP + CHX rinse |
| 4. Supragingival cleaning | 16. SRP + AV gel |
| 5. Supragingival cleaning + AZM | 17. SRP + AZM gel |
| 6. Doxy | 18. SRP + ALN gel |
| 7. OHI + SRP | 19. SRP + SMV gel |
| 8. SRP + SDD | 20. SRP + CLM gel |
| 9. SRP + Doxy | 21. SRP + EO-based rinse |
| 10. SRP + AZM | 22. SRP + TET (topical) |
| 11. SRP + MTZ + AMX | 23. SRP + TET (topical) + intensive maintenance |
| 12. SRP + powered subgingival water irrigation | 24. SRP + CHX rinse + Doxy |

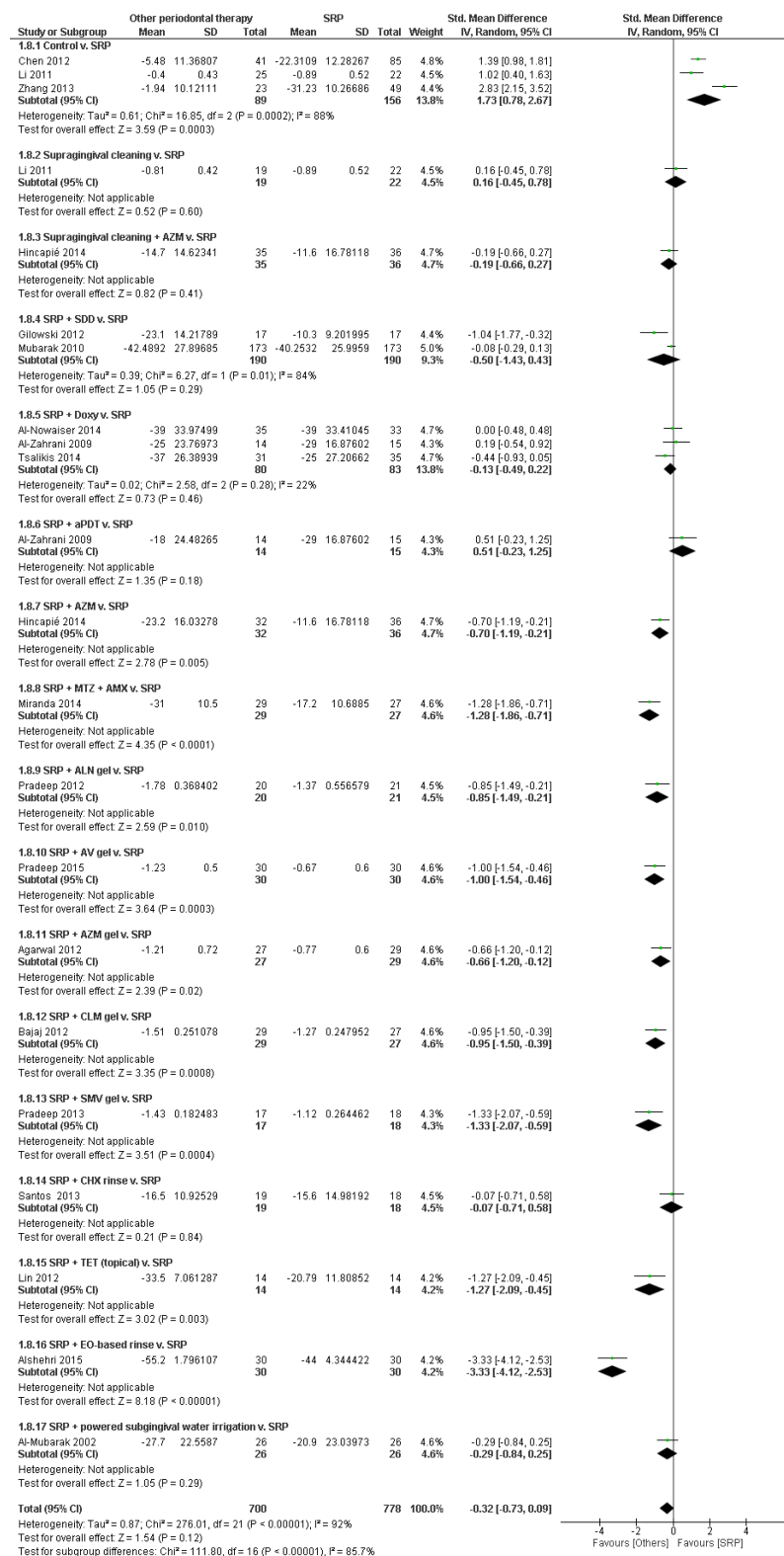
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

Direct evidence (Figure 3.9) was congruent with estimates from the fixed-effects model, in which several treatments appeared significantly better than SRP; however these effects were not conserved in the random-effects model. Based on DIC and total residual deviance, the random-effects model was considered to be a better fit (Table 3.36).

TABLE 3.36 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR BOP AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	1.73* (0.78 to 2.67)	3	88%	1.54* (0.48 to 2.64)	1.39* (1.12 to 1.67)
Supragingival cleaning	SRP	0.16 (-0.45 to 0.78)	1	NA	0.42 (-1.42 to 2.28)	0.35 (-0.19 to 0.89)
Supragingival cleaning + AZM	SRP	-0.19 (-0.66 to 0.27)	1	NA	-0.20 (-2.25 to 1.81)	-0.20 (-0.66 to 0.26)
SRP + SDD	SRP	-0.50 (-1.43 to 0.43)	2	84%	-0.52 (-2.00 to 0.90)	-0.16 (-0.37 to 0.04)
SRP + Doxy	SRP	-0.13 (-0.49 to 0.22)	3	22%	-0.10 (-1.28 to 1.09)	-0.14 (-0.45 to 0.16)
SRP + aPDT	SRP	0.51 (-0.23 to 1.25)	1	NA	0.36 (-1.54 to 2.28)	0.34 (-0.30 to 0.99)
SRP + AZM	SRP	-0.70* (-1.19 to -0.21)	1	NA	-0.71 (-2.73 to 1.30)	-0.70* (-1.19 to -0.21)
SRP + MTZ + AMX	SRP	-1.28* (-1.86 to -0.71)	1	NA	-1.28 (-3.33 to 0.75)	-1.29* (-1.85 to -0.72)
SRP + ALN gel	SRP	-0.85* (-1.49 to -0.21)	1	NA	-0.84 (-2.91 to 1.21)	-0.85* (-1.48 to -0.22)
SRP + AV gel	SRP	-1.00* (-1.54 to -0.46)	1	NA	-1.01 (-3.07 to 1.02)	-1.00* (-1.53 to -0.47)
SRP + AZM gel	SRP	-0.66* (-1.20 to -0.12)	1	NA	-0.66 (-2.67 to 1.37)	-0.66* (-1.19 to -0.13)
SRP + CLM gel	SRP	-0.95* (-1.50 to -0.39)	1	NA	-0.95 (-2.96 to 1.04)	-0.95* (-1.49 to -0.40)
SRP + SMV gel	SRP	-1.33* (-2.07 to -0.59)	1	NA	-1.33 (-3.42 to 0.72)	-1.33* (-2.04 to -0.62)
SRP + CHX rinse	SRP	-0.07 (-0.71 to 0.58)	1	NA	0.52 (-0.99 to 2.00)	0.79* (0.48 to 1.10)
SRP + TET (topical)	SRP	-1.27* (-2.09 to -0.45)	1	NA	-1.27 (-3.40 to 0.85)	-1.27* (-2.05 to -0.48)
SRP + EO-based rinse	SRP	-3.33* (-4.12 to -2.53)	1	NA	-3.32* (-5.39 to -1.22)	-3.32* (-4.10 to -2.55)
SRP + powered subgingival water irrigation	SRP	-0.29 (-0.84 to 0.25)	1	NA	-0.30 (-2.35 to 1.68)	-0.29 (-0.83 to 0.24)
				DIC	35.617	60.148
				Total residual deviance (Unconstrained data points)	29.33 (55 points)	59.38 (55 points)
Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.						

FIGURE 3.9 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON BOP AT 3 MONTHS



End of study

The evidence network for BOP by the end of the study included 30 trials, 2430 participants and 29 treatments providing 43 comparisons based on 25 trials with 2 arms, 4 trials with 3 arms and 1 trial with 4 arms. Four trials that had reported BOP were not included in this network. Two trials compared FMSRP with PMSRP (Santos 2012; Santos 2009) and 2 trials were not connected to the network (Raman 2014; Llambés 2012/2008/2005). There was no evidence of inconsistency in the network (Figure A8.28).

Compared with control/no treatment and supragingival cleaning, SRP was significantly better at improving (lowering) BOP. Two treatments, “SRP plus EO-based rinse” and “SRP plus SMV gel”, showed a significantly better effect than SRP (Table 3.37-3.38).

In the direct evidence (Figure 3.10), the difference between supragingival cleaning and SRP was not significant, which was inconsistent with estimates from both fixed- and random- effects models. Several therapies appeared to have significantly better effect than SRP in both the fixed-effects model and direct evidence; however, these significant differences were not conserved in the random-effects network model. Based on DIC and total residual deviance, the random-effects model was considered to be a better fit (Table 3.39).

TABLE 3.37 BOP----- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	1.89* (0.52)	—								
3	1.40* (0.55)	-0.48 (0.61)	—							
4	0.41 (0.85)	-1.48 (0.99)	-0.99 (1.01)	—						
5	0.64 (1.00)	-1.24 (1.13)	-0.76 (1.14)	0.23 (1.31)	—					
6	-0.30 (0.86)	-2.18* (1.00)	-1.70 (1.02)	-0.71 (1.21)	-0.94 (1.32)	—				
7	-0.32 (0.58)	-2.21* (0.73)	-1.73* (0.75)	-0.73 (1.03)	-0.97 (1.15)	-0.03 (1.04)	—			
8	-0.22 (0.50)	-2.11* (0.72)	-1.62* (0.74)	-0.63 (0.98)	-0.86 (0.87)	0.08 (0.99)	0.10 (0.76)	—		
9	-0.17 (0.85)	-2.06* (0.99)	-1.57 (1.01)	-0.58 (0.85)	-0.82 (1.31)	0.12 (1.21)	0.15 (1.03)	0.05 (0.98)	—	
10	-1.06	-2.95*	-2.47*	-1.48	-1.71	-0.77	-0.74	-0.85	-0.89	—

	(0.87)	(1.02)	(1.03)	(1.22)	(1.32)	(1.22)	(1.05)	(1.00)	(1.21)	
11	0.31 (0.81)	-1.58 (0.97)	-1.09 (0.97)	-0.10 (1.17)	-0.34 (1.19)	0.60 (1.18)	0.63 (0.99)	0.53 (0.81)	0.48 (1.16)	1.37 (1.19)
12	0.34 (0.53)	-1.55* (0.53)	-1.07 (0.59)	-0.07 (1.00)	-0.31 (1.13)	0.63 (1.01)	0.66 (0.67)	0.56 (0.73)	0.51 (1.00)	1.40 (1.02)
13	0.54 (0.87)	-1.35 (0.78)	-0.86 (0.92)	0.13 (1.21)	-0.10 (1.33)	0.84 (1.22)	0.86 (0.99)	0.76 (1.00)	0.71 (1.22)	1.60 (1.24)
14	-1.59 (1.02)	-3.48* (0.87)	-2.99* (1.06)	-2.00 (1.32)	-2.23 (1.43)	-1.29 (1.34)	-1.27 (1.14)	-1.37 (1.13)	-1.42 (1.32)	-0.52 (1.35)
15	0.25 (0.74)	-1.64 (0.83)	-1.16 (0.86)	-0.17 (1.13)	-0.40 (1.24)	0.54 (1.13)	0.57 (0.78)	0.46 (0.88)	0.42 (1.12)	1.31 (1.14)
16	-0.30 (1.04)	-2.19* (1.04)	-1.70 (1.07)	-0.71 (1.34)	-0.94 (1.44)	0.00 (1.35)	0.02 (1.12)	-0.08 (1.15)	-0.13 (1.34)	0.77 (1.35)
17	0.14 (1.04)	-1.75 (1.04)	-1.27 (1.06)	-0.28 (1.34)	-0.51 (1.45)	0.43 (1.35)	0.46 (1.11)	0.35 (1.15)	0.31 (1.34)	1.20 (1.37)
18	-0.92 (1.02)	-2.81* (1.01)	-2.32* (1.05)	-1.33 (1.32)	-1.56 (1.43)	-0.62 (1.32)	-0.60 (1.10)	-0.70 (1.13)	-0.75 (1.32)	0.14 (1.34)
19	0.09 (1.36)	-1.80 (1.36)	-1.31 (1.39)	-0.32 (1.61)	-0.55 (1.68)	0.39 (1.61)	0.41 (1.43)	0.31 (1.44)	0.26 (1.60)	1.15 (1.62)
20	-0.29 (0.98)	-2.18* (0.84)	-1.69 (1.04)	-0.70 (1.29)	-0.93 (1.40)	0.01 (1.30)	0.03 (1.11)	-0.07 (1.10)	-0.12 (1.30)	0.77 (1.32)
21	-3.31* (0.90)	-5.20* (1.04)	-4.71* (1.06)	-3.72* (1.23)	-3.96* (1.35)	-3.02* (1.24)	-2.99* (1.08)	-3.09* (1.03)	-3.14* (1.23)	-2.25 (1.25)
22	-4.42* (1.02)	-6.30* (1.15)	-5.82* (1.16)	-4.83* (1.33)	-5.06* (1.42)	-4.12* (1.33)	-4.09* (1.17)	-4.20* (1.14)	-4.24* (1.33)	-3.35* (1.34)
23	-0.78 (0.86)	-2.67* (1.01)	-2.18* (1.02)	-1.19 (1.20)	-1.42 (1.32)	-0.48 (1.21)	-0.46 (1.04)	-0.56 (0.99)	-0.61 (1.19)	0.29 (1.23)
24	-0.36 (0.85)	-2.25* (1.00)	-1.77 (1.01)	-0.78 (1.20)	-1.01 (1.32)	-0.07 (1.21)	-0.04 (1.03)	-0.15 (0.99)	-0.19 (1.20)	0.70 (1.22)
25	-0.67 (0.86)	-2.56* (1.00)	-2.07* (1.02)	-1.08 (1.20)	-1.31 (1.31)	-0.37 (1.22)	-0.35 (1.04)	-0.45 (0.99)	-0.50 (1.20)	0.40 (1.23)
26	-1.36 (0.88)	-3.24* (1.02)	-2.76* (1.04)	-1.77 (1.23)	-2.00 (1.33)	-1.06 (1.24)	-1.03 (1.06)	-1.14 (1.02)	-1.18 (1.23)	-0.29 (1.24)
27	-1.16 (0.91)	-3.05* (1.05)	-2.56* (1.06)	-1.57 (1.24)	-1.81 (1.35)	-0.87 (1.25)	-0.84 (1.08)	-0.94 (1.04)	-0.99 (1.24)	-0.10 (1.26)
28	0.57 (1.01)	-1.32 (0.87)	-0.83 (1.07)	0.16 (1.32)	-0.07 (1.42)	0.87 (1.33)	0.89 (1.13)	0.79 (1.13)	0.74 (1.32)	1.63 (1.34)
29	1.06 (0.75)	-0.83 (0.64)	-0.34 (0.80)	0.65 (1.13)	0.42 (1.25)	1.36 (1.14)	1.38 (0.88)	1.28 (0.90)	1.23 (1.13)	2.12 (1.16)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.03 (0.97)	—								
13	0.23 (1.19)	0.20 (0.79)	—							
14	-1.90 (1.30)	-1.93 (1.02)	-2.13 (1.18)	—						
15	-0.06 (1.09)	-0.09 (0.76)	-0.30 (1.06)	1.83 (1.21)	—					
16	-0.61 (1.32)	-0.64 (0.89)	-0.84 (1.19)	1.29 (1.35)	-0.54 (1.17)	—				
17	-0.17 (1.31)	-0.20 (0.89)	-0.40 (1.19)	1.72 (1.35)	-0.11 (1.17)	0.43 (1.26)	—			
18	-1.23 (1.29)	-1.26 (0.87)	-1.46 (1.18)	0.67 (1.35)	-1.17 (1.15)	-0.62 (1.24)	-1.06 (1.25)	—		
19	-0.22 (1.58)	-0.25 (1.25)	-0.45 (1.48)	1.68 (1.61)	-0.16 (1.46)	0.39 (0.88)	-0.05 (1.54)	1.01 (1.52)	—	
20	-0.60 (1.28)	-0.63 (0.99)	-0.83 (1.15)	1.30 (1.21)	-0.54 (1.18)	0.01 (1.34)	-0.43 (1.34)	0.63 (1.31)	-0.38 (1.60)	—
21	-3.62* (1.21)	-3.65* (1.04)	-3.85* (1.26)	-1.72 (1.35)	-3.56* (1.17)	-3.01* (1.37)	-3.45* (1.37)	-2.39 (1.35)	-3.40* (1.63)	-3.02* (1.33)
22	-4.72* (1.30)	-4.75* (1.16)	-4.96* (1.35)	-2.83 (1.45)	-4.66* (1.26)	-4.12* (1.47)	-4.55* (1.47)	-3.50* (1.45)	-4.51* (1.72)	-4.13* (1.41)

23	-1.09 (1.17)	-1.12 (1.01)	-1.32 (1.22)	0.81 (1.33)	-1.02 (1.13)	-0.48 (1.35)	-0.91 (1.34)	0.14 (1.33)	-0.87 (1.61)	-0.49 (1.31)
24	-0.67 (1.17)	-0.70 (1.01)	-0.91 (1.22)	1.22 (1.33)	-0.61 (1.13)	-0.07 (1.35)	-0.50 (1.35)	0.55 (1.32)	-0.45 (1.61)	-0.07 (1.29)
25	-0.98 (1.18)	-1.01 (1.01)	-1.21 (1.23)	0.92 (1.33)	-0.91 (1.13)	-0.37 (1.35)	-0.80 (1.35)	0.25 (1.33)	-0.76 (1.62)	-0.38 (1.30)
26	-1.66 (1.19)	-1.69 (1.03)	-1.90 (1.24)	0.23 (1.34)	-1.60 (1.15)	-1.06 (1.36)	-1.49 (1.36)	-0.44 (1.34)	-1.45 (1.63)	-1.07 (1.32)
27	-1.47 (1.23)	-1.50 (1.06)	-1.70 (1.26)	0.43 (1.37)	-1.41 (1.17)	-0.86 (1.39)	-1.30 (1.38)	-0.24 (1.37)	-1.25 (1.64)	-0.87 (1.35)
28	0.26 (1.31)	0.23 (1.02)	0.03 (1.17)	2.16 (1.24)	0.33 (1.21)	0.87 (1.36)	0.43 (1.36)	1.49 (1.34)	0.48 (1.63)	0.86 (1.21)
29	0.75 (1.10)	0.72 (0.66)	0.52 (0.95)	2.65* (1.08)	0.82 (0.96)	1.36 (1.11)	0.92 (1.11)	1.98 (1.08)	0.97 (1.41)	1.35 (1.06)
Treatment	21	22	23	24	25	26	27	28	29	
21	—									
22	-1.10 (1.37)	—								
23	2.53* (1.23)	3.64* (1.34)	—							
24	2.95* (1.24)	4.05* (1.32)	0.41 (1.20)	—						
25	2.64* (1.24)	3.75* (1.33)	0.11 (1.22)	-0.30 (1.21)	—					
26	1.96 (1.26)	3.06* (1.35)	-0.58 (1.23)	-0.99 (1.23)	-0.69 (1.23)	—				
27	2.15 (1.28)	3.25* (1.37)	-0.38 (1.25)	-0.80 (1.25)	-0.49 (1.25)	0.19 (1.26)	—			
28	3.88* (1.35)	4.99* (1.45)	1.35 (1.33)	0.94 (1.32)	1.24 (1.33)	1.93 (1.34)	1.73 (1.37)	—		
29	4.37* (1.17)	5.48* (1.28)	1.84 (1.13)	1.43 (1.14)	1.73 (1.14)	2.42* (1.16)	2.22 (1.18)	0.49 (1.09)	—	

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 16. SRP + Doxy+ intensive maintenance |
| 2. Control/no treatment | 17. SRP + AMX+ intensive maintenance |
| 3. Supragingival cleaning | 18. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning + AZM | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 5. Doxy | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. SRP + powered subgingival water irrigation | 21. SRP + EO-based rinse |
| 7. SRP + SDD | 22. SRP + SMV gel |
| 8. SRP + Doxy | 23. SRP + CLM gel |
| 9. SRP + AZM | 24. SRP + AV gel |
| 10. SRP + ALN | 25. SRP + AZM gel |
| 11. SRP + aPDT | 26. SRP + ALN gel |
| 12. SRP + intensive maintenance | 27. SRP + TET (topical) |
| 13. SRP + non-intensive maintenance | 28. SRP + TET (topical) + intensive maintenance |
| 14. OHI+ SRP+ intensive maintenance | 29. SRP + CHX rinse + intensive maintenance |
| 15. SRP + SDD + intensive maintenance | |

**TABLE 3.38 BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

Treatment**	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	26	27	28	29
1																													
2																													
3																													
4																													
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**Legend:

- | | |
|---|---|
| 1. SRP | 16. SRP + Doxy+ intensive maintenance |
| 2. Control/no treatment | 17. SRP + AMX+ intensive maintenance |
| 3. Supragingival cleaning | 18. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning + AZM | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 5. Doxy | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. SRP + powered subgingival water irrigation | 21. SRP + EO-based rinse |
| 7. SRP + SDD | 22. SRP + SMV gel |
| 8. SRP + Doxy | 23. SRP + CLM gel |
| 9. SRP + AZM | 24. SRP + AV gel |
| 10. SRP + ALN | 25. SRP + AZM gel |
| 11. SRP + aPDT | 26. SRP + ALN gel |
| 12. SRP + intensive maintenance | 27. SRP + TET (topical) |
| 13. SRP + non-intensive maintenance | 28. SRP + TET (topical) + intensive maintenance |
| 14. OHI+ SRP+ intensive maintenance | 29. SRP + CHX rinse + intensive maintenance |
| 15. SRP + SDD + intensive maintenance | |

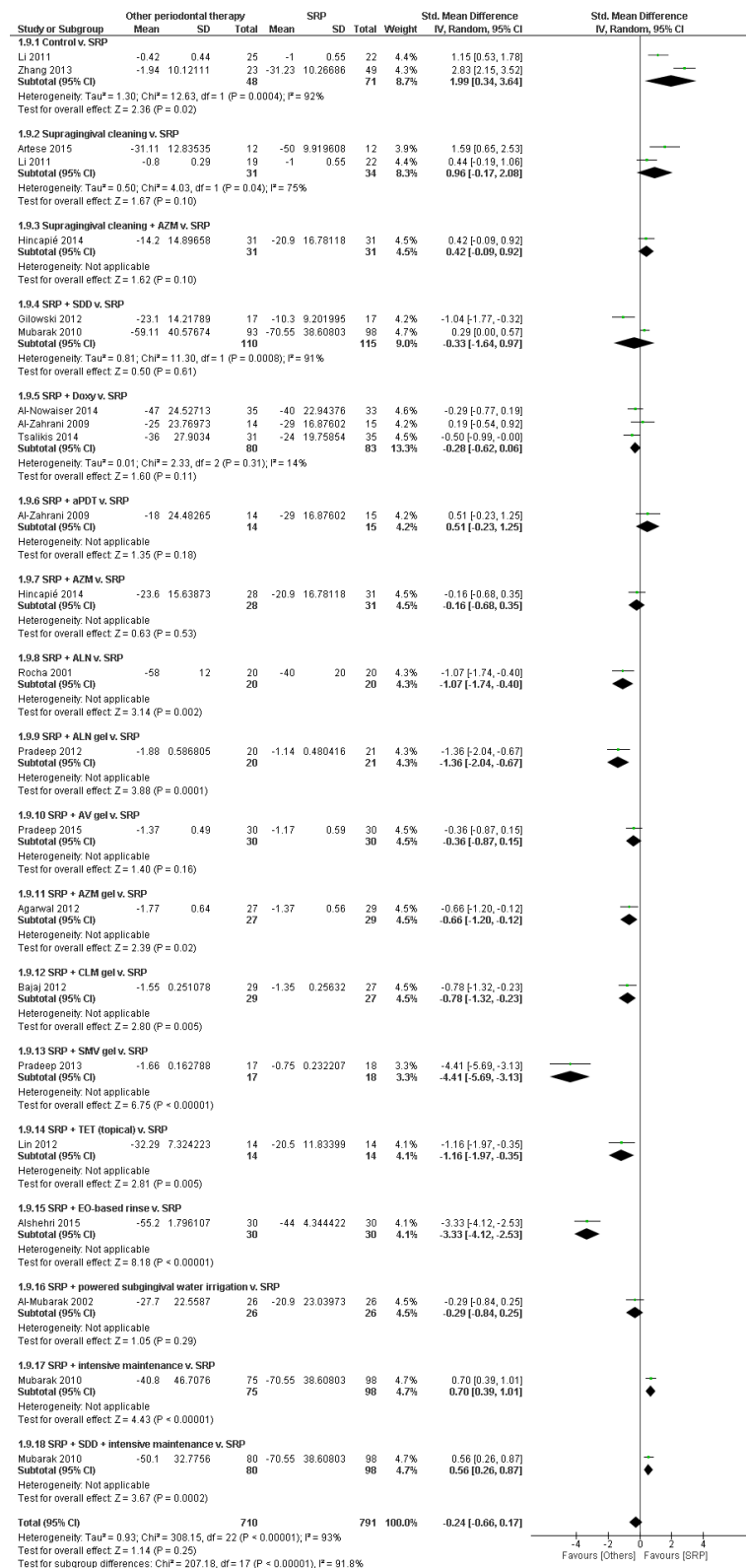
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.39 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR BOP AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	1.99* (0.34 to 3.64)	2	92%	1.89* (0.85 to 2.92)	1.89* (1.56 to 2.22)
Supragingival cleaning	SRP	0.96 (-0.17 to 2.08)	2	75%	1.40* (0.32 to 2.49)	1.46* (1.07 to 1.86)
Supragingival cleaning + AZM	SRP	0.42 (-0.09 to 0.92)	1	NA	0.41 (-1.29 to 2.11)	0.42 (-0.08 to 0.91)
SRP + SDD	SRP	-0.33 (-1.64 to 0.97)	2	91%	-0.32 (-1.50 to 0.83)	0.06 (-0.19 to 0.32)
SRP + Doxy	SRP	-0.28 (-0.62 to 0.06)	3	14%	-0.22 (-1.20 to 0.78)	-0.28 (-0.59 to 0.02)
SRP + aPDT	SRP	0.51 (-0.23 to 1.25)	1	NA	0.31 (-1.28 to 1.96)	0.27 (-0.37 to 0.91)
SRP + AZM	SRP	-0.16 (-0.68 to 0.35)	1	NA	-0.17 (-1.91 to 1.51)	-0.17 (-0.68 to 0.34)
SRP + ALN	SRP	-1.07* (-1.74 to -0.40)	1	NA	-1.03 (-2.77 to 0.04)	-1.07* (-1.73 to -0.42)
SRP + ALN gel	SRP	-1.36* (-2.04 to -0.67)	1	NA	-1.36 (-3.10 to 0.43)	-1.36* (-2.03 to -0.69)
SRP + AV gel	SRP	-0.36* (-0.87 to 0.15)	1	NA	-0.36 (-2.08 to 1.35)	-0.36 (-0.87 to 0.14)
SRP + AZM gel	SRP	-0.66* (-1.20 to -0.12)	1	NA	-0.67 (-2.39 to 1.04)	-0.66* (-1.19 to -0.13)
SRP + CLM gel	SRP	-0.78* (-1.32 to -0.23)	1	NA	-0.78 (-2.47 to 0.94)	-0.78* (-1.32 to -0.24)
SRP + SMV gel	SRP	-4.41* (-5.69 to -3.13)	1	NA	-4.42* (-6.40 to -2.40)	-4.41* (-5.61 to -3.21)
SRP + TET (topical)	SRP	-1.16* (-1.97 to -0.35)	1	NA	-1.16 (-2.94 to 0.63)	-1.16* (-1.94 to -0.39)
SRP + EO-based rinse	SRP	-3.33* (-4.12 to -2.53)	1	NA	-3.31* (-5.07 to -1.52)	-3.33* (-4.10 to -2.55)
SRP + powered subgingival water irrigation	SRP	-0.29 (-0.84 to 0.25)	1	NA	-0.30 (-1.99 to 1.41)	-0.29 (-0.83 to 0.24)
SRP + intensive maintenance	SRP	0.70 (0.39 to 1.01)	1	NA	0.34 (-0.72 to 1.41)	0.51* (0.25 to 0.77)
SRP + SDD + intensive maintenance	SRP	0.56* (0.26 to 0.87)	1	NA	0.25 (-1.21 to 1.72)	0.44* (0.14 to 0.72)
DIC					45.633	75.289
Total residual deviance (Unconstrained data points)					36.33 (66 points)	73.04 (66 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.10 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON BOP AT END OF STUDY



3.2.6 PLAQUE INDEX (PI)

3 months

Thirty-seven trials reported the outcome of PI. The evidence network for PI at 3 months included 31 trials and 2496 participants, providing 41 comparisons based on 26 trials with 2 arms and 5 trials with 3 arms. Six trials were not included in this network meta-analysis. One trial did not provide data at 3 month (Artese 2015); 2 trials compared FMSRP with PMSRP (Santos 2012; Santos 2009) and 3 trials were not connected to the network (Macedo 2014; O'Connell 2008; Rodrigues 2003). There was no evidence of inconsistency in the network (Figure A8.29).

The results showed that SRP had a significant effect on improving PI. One treatment ("SRP plus EO-based rinse) had a significantly better effect than SRP (Table 3.40-3.41). In the direct evidence (Figure 3.11), 3 treatments appeared to be significantly better than SRP. The significant effect could be found in the fixed-effects model but not in the random-effects model. Interestingly, in the fixed-effects model, SRP plus CHX rinse showed a worse outcome than SRP. Based on DIC and total residual deviance, the random-effects model appeared to be a better fit (Table 3.42).

TABLE 3.40 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	2.35* (0.84)	—								
3	-0.40 (2.41)	-2.75 (2.36)	—							
4	-1.42 (2.10)	-3.78 (1.97)	-1.03 (2.87)	—						
5	0.78 (1.81)	-1.57 (1.81)	1.18 (2.93)	2.21 (2.66)	—					
6	0.09 (1.99)	-2.26 (2.15)	0.49 (3.13)	1.51 (2.89)	-0.69 (2.69)	—				
7	2.86 (2.25)	0.51 (2.37)	3.26 (3.28)	4.28 (3.05)	2.08 (2.87)	2.77 (3.00)	—			
8	-3.09 (2.20)	-5.44* (2.04)	-2.70 (3.13)	-1.67 (2.84)	-3.88 (2.73)	-3.18 (2.96)	-5.95 (3.12)	—		
9	-1.44 (2.04)	-3.79 (2.21)	-1.04 (3.17)	-0.01 (2.93)	-2.22 (2.70)	-1.53 (2.84)	-4.30 (3.04)	1.65 (3.01)	—	
10	-0.38 (1.42)	-2.73 (1.65)	0.01 (2.80)	1.04 (2.53)	-1.16 (2.30)	-0.47 (2.44)	-3.24 (2.65)	2.71 (2.61)	1.06 (2.49)	—
11	-0.19 (0.97)	-2.54* (1.22)	0.20 (2.58)	1.23 (2.28)	-0.97 (2.03)	-0.28 (2.21)	-3.05 (2.04)	2.90 (2.36)	1.25 (2.26)	0.19 (1.72)
12	0.15 (2.00)	-2.21 (2.17)	0.54 (3.13)	1.57 (2.89)	-0.64 (2.70)	0.05 (2.00)	-2.71 (3.02)	3.24 (2.98)	1.58 (2.84)	0.53 (2.45)
13	-0.24 (2.02)	-2.59 (2.18)	0.16 (3.13)	1.18 (2.90)	-1.02 (2.70)	-0.33 (2.83)	-3.10 (3.03)	2.85 (2.98)	1.20 (2.86)	0.14 (2.47)
14	-0.10 (1.83)	-2.45 (1.99)	0.29 (3.00)	1.32 (2.78)	-0.89 (2.55)	-0.19 (2.70)	-2.96 (2.73)	2.99 (2.83)	1.34 (2.74)	0.28 (2.32)
15	0.45 (2.19)	-1.90 (2.02)	0.85 (3.11)	1.88 (2.83)	-0.33 (2.71)	0.36 (2.95)	-2.41 (3.12)	3.55 (2.86)	1.89 (3.00)	0.84 (2.60)
16	-0.97 (1.31)	-3.33* (1.22)	-0.58 (2.03)	0.45 (2.02)	-1.76 (2.12)	-1.06 (2.38)	-3.83 (2.58)	2.12 (2.37)	0.46 (2.43)	-0.59 (1.93)
17	0.46 (2.02)	-1.89 (2.18)	0.86 (3.14)	1.88 (2.91)	-0.32 (2.71)	0.37 (2.85)	-2.40 (3.04)	3.55 (2.98)	1.90 (2.87)	0.84 (2.49)
18	-1.06 (2.01)	-3.41 (2.18)	-0.66 (3.14)	0.37 (2.89)	-1.84 (2.70)	-1.15 (2.84)	-3.92 (3.02)	2.03 (2.98)	0.38 (2.85)	-0.68 (2.46)
19	-0.30 (2.01)	-2.65 (2.18)	0.10 (3.14)	1.13 (2.89)	-1.08 (2.69)	-0.39 (2.82)	-3.15 (3.06)	2.80 (2.98)	1.14 (2.87)	0.09 (2.46)
20	-0.31 (2.02)	-2.66 (2.19)	0.08 (3.14)	1.11 (2.90)	-1.10 (2.73)	-0.40 (2.86)	-3.17 (3.02)	2.78 (2.99)	1.13 (2.87)	0.07 (2.48)
21	-0.59 (2.03)	-2.94 (2.19)	-0.19 (3.14)	0.84 (2.90)	-1.37 (2.70)	-0.68 (2.85)	-3.44 (3.03)	2.51 (3.00)	0.85 (2.87)	-0.20 (2.49)
22	-0.26 (2.01)	-2.61 (2.17)	0.14 (3.13)	1.17 (2.90)	-1.04 (2.70)	-0.35 (2.83)	-3.12 (3.03)	2.84 (2.98)	1.18 (2.87)	0.13 (2.45)
23	-5.17* (2.06)	-7.52* (2.22)	-4.78 (3.17)	-3.75 (2.94)	-5.96* (2.73)	-5.26 (2.87)	-8.03* (3.05)	-2.08 (3.01)	-3.74 (2.90)	-4.79 (2.49)
24	-0.15 (1.19)	-2.50 (1.45)	0.25 (2.69)	1.28 (2.40)	-0.93 (2.15)	-0.24 (2.30)	-3.01 (2.56)	2.94 (2.50)	1.29 (2.36)	0.23 (1.85)
25	-1.18 (2.36)	-3.53 (2.32)	-0.78 (2.85)	0.24 (2.82)	-1.96 (2.90)	-1.27 (3.09)	-4.04 (3.25)	1.91 (3.10)	0.26 (3.13)	-0.80 (2.76)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.34 (2.23)	—								
13	-0.05 (2.24)	-0.39 (2.83)	—							
14	0.09 (1.83)	-0.25 (2.72)	0.14 (2.72)	—						
15	0.65	0.31	0.69	0.56	—					

	(2.36)	(2.96)	(2.97)	(2.83)						
16	-0.78 (1.60)	-1.12 (2.39)	-0.73 (2.40)	-0.87 (2.23)	-1.43 (2.38)	—				
17	0.65 (2.25)	0.32 (2.84)	0.70 (2.86)	0.56 (2.75)	0.01 (2.96)	1.43 (2.40)	—			
18	-0.87 (2.24)	-1.20 (2.84)	-0.82 (2.86)	-0.95 (2.74)	-1.51 (2.96)	-0.08 (2.39)	-1.52 (2.83)	—		
19	-0.10 (2.25)	-0.44 (2.83)	-0.05 (2.84)	-0.19 (2.70)	-0.75 (2.99)	0.68 (2.41)	-0.76 (2.85)	0.76 (2.85)	—	
20	-0.12 (2.24)	-0.46 (2.86)	-0.07 (2.87)	-0.21 (2.73)	-0.77 (2.98)	0.66 (2.40)	-0.77 (2.86)	0.75 (2.87)	-0.02 (2.86)	—
21	-0.39 (2.24)	-0.73 (2.85)	-0.34 (2.86)	-0.48 (2.71)	-1.04 (2.99)	0.39 (2.41)	-1.05 (2.86)	0.47 (2.85)	-0.29 (2.86)	-0.27 (2.87)
22	-0.06 (2.23)	-0.40 (2.84)	-0.02 (2.85)	-0.15 (2.72)	-0.71 (2.97)	0.72 (2.39)	-0.72 (2.86)	0.80 (2.84)	0.04 (2.83)	0.06 (2.87)
23	-4.98* (2.27)	-5.32 (2.88)	-4.93 (2.89)	-5.07 (2.73)	-5.63 (3.00)	-4.20 (2.43)	-5.63 (2.90)	-4.12 (2.88)	-4.88 (2.88)	-4.86 (2.88)
24	0.04 (1.54)	-0.29 (2.32)	0.09 (2.34)	-0.05 (2.18)	-0.60 (2.50)	0.83 (1.77)	-0.61 (2.34)	0.91 (2.34)	0.15 (2.33)	0.16 (2.36)
25	-0.99 (2.54)	-1.33 (3.10)	-0.94 (3.10)	-1.08 (2.97)	-1.63 (3.09)	-0.21 (1.99)	-1.64 (3.10)	-0.12 (3.09)	-0.88 (3.12)	-0.87 (3.12)
Treatment	21	22	23	24	25					
21	—									
22	0.33 (2.85)	—								
23	-4.59 (2.89)	-4.92 (2.87)	—							
24	0.44 (2.34)	0.11 (2.33)	5.03* (2.38)	—						
25	-0.59 (3.09)	-0.92 (3.10)	3.99 (3.14)	-1.03 (2.65)	—					

* Statistically significant

**Legend:

- | | | |
|---|---|----------------------------|
| 1. SRP | 10. SRP + SDD | 19. SRP + AZM gel |
| 2. Control/no treatment | 11. SRP + Doxy | 20. SRP + ALN gel |
| 3. Intensive OHI | 12. SRP + AZM | 21. SRP + SMV gel |
| 4. CHX rinse | 13. SRP + MTZ + AMX | 22. SRP + CLM gel |
| 5. Supragingival cleaning | 14. SRP + aPDT | 23. SRP + EO-based rinse |
| 6. Supragingival cleaning + AZM | 15. SRP/flap surgery+ Tinidazole + Ampicillin | 24. SRP + TET (topical) |
| 7. Doxy | 16. SRP + CHX rinse | 25. SRP + CHX rinse + Doxy |
| 8. OHI + SRP | 17. SRP + SZ gel | |
| 9. SRP + powered subgingival water irrigation | 18. SRP + AV gel | |

TABLE 3.41 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

Treatment**	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																									
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25																									

**Legend:

- | | | |
|---|---|----------------------------|
| 1. SRP | 10. SRP + SDD | 19. SRP + AZM gel |
| 2. Control/no treatment | 11. SRP + Doxy | 20. SRP + ALN gel |
| 3. Intensive OHI | 12. SRP + AZM | 21. SRP + SMV gel |
| 4. CHX rinse | 13. SRP + MTZ + AMX | 22. SRP + CLM gel |
| 5. Supragingival cleaning | 14. SRP + aPDT | 23. SRP + EO-based rinse |
| 6. Supragingival cleaning + AZM | 15. SRP/flap surgery+ Tinidazole + Ampicillin | 24. SRP + TET (topical) |
| 7. Doxy | 16. SRP + CHX rinse | 25. SRP + CHX rinse + Doxy |
| 8. OHI + SRP | 17. SRP + SZ gel | |
| 9. SRP + powered subgingival water irrigation | 18. SRP + AV gel | |

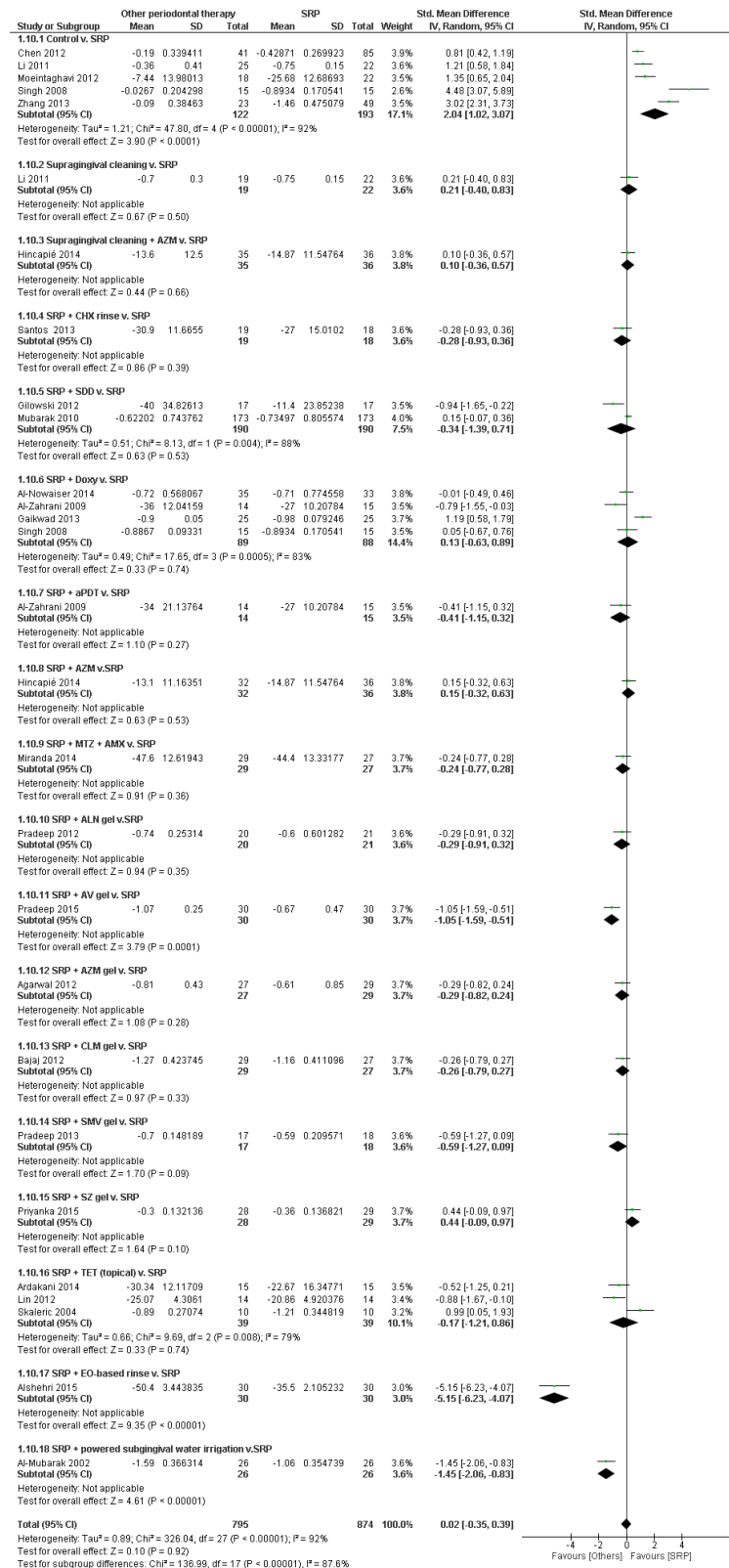
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.42 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PI AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	2.04* (1.02 to 3.07)	5	92%	2.35* (0.68 to 4.03)	1.29* (1.04 to 1.54)
Supragingival cleaning	SRP	0.21 (-0.40 to 0.83)	1	NA	0.78 (-2.80 to 4.42)	0.25 (-0.30 to 0.79)
Supragingival cleaning + AZM	SRP	0.10 (-0.36 to 0.57)	1	NA	0.09 (-3.91 to 4.07)	0.10 (-0.36 to 0.56)
SRP + CHX rinse	SRP	-0.28 (-0.93 to 0.36)	1	NA	-0.97 (-3.62 to 1.56)	0.66* (0.36 to 0.94)
SRP + SDD	SRP	-0.34 (-1.39 to 0.71)	2	88%	-0.38 (-3.25 to 2.48)	0.05 (-0.15 to 0.26)
SRP + Doxy	SRP	0.13 (-0.63 to 0.89)	4	83%	-0.19 (-2.14 to 1.77)	0.08 (-0.21 to 0.37)
SRP + aPDT	SRP	-0.41 (-1.15 to 0.32)	1	NA	-0.10 (-3.77 to 3.52)	-0.01 (-0.64 to 0.64)
SRP + AZM	SRP	0.15 (-0.32 to 0.63)	1	NA	0.15 (-3.86 to 4.09)	0.15 (-0.31 to 0.62)
SRP + MTZ + AMX	SRP	-0.24 (-0.77 to 0.28)	1	NA	-0.24 (-4.24 to 3.80)	-0.24 (-0.77 to 0.28)
SRP + ALN gel	SRP	-0.29 (-0.91 to 0.32)	1	NA	-0.31 (-4.34 to 3.74)	-0.29 (-0.91 to 0.31)
SRP + AV gel	SRP	-1.05* (-1.59 to -0.51)	1	NA	-1.06 (-5.05 to 2.94)	-1.05 (-1.58 to -0.52)
SRP + AZM gel	SRP	-0.29 (-0.82 to 0.24)	1	NA	-0.30 (-4.28 to 3.73)	-0.29 (-0.81 to 0.22)
SRP + CLM gel	SRP	-0.26 (-0.79 to 0.27)	1	NA	-0.26 (-4.24 to 3.74)	-0.26 (-0.78 to 0.26)
SRP + SMV gel	SRP	-0.59 (-1.27 to 0.09)	1	NA	-0.59 (-4.71 to 3.43)	-0.59 (-1.25 to 0.07)
SRP + SZ gel	SRP	0.44 (-0.09 to 0.97)	1	NA	0.46 (-3.58 to 4.51)	0.44 (-0.08 to 0.96)
SRP + TET (topical)	SRP	-0.17 (-1.21 to 0.86)	3	79%	-0.15 (-2.51 to 2.22)	-0.27 (-0.71 to 0.18)
SRP + EO-based rinse	SRP	-5.15* (-6.23 to -4.07)	1	NA	-5.17* (-9.29 to -1.07)	-5.16* (-6.20 to -4.13)
SRP + powered subgingival water irrigation	SRP	-1.45* (-2.06 to -0.83)	1	NA	-1.44 (-5.47 to 2.61)	-1.45* (-2.05 to -0.85)
DIC					37.01	197.538
Total residual deviance (Unconstrained data points)					55.079 (67 points)	191.1 (67 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.11 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PI AT 3 MONTHS



End of study

The evidence network for PI by the end of study included 2610 participants and 33 treatments providing 52 comparisons based on 28 trials with 2 arms, 6 trials with 3 arms, and 1 trial with 4 arms. Two trials that had reported the outcome of PI were not included in this network meta-analysis for comparing FMSRP with PMSRP (Santos 2012; Santos 2009). There was no evidence of inconsistency in the network (Figure A8.30).

Compared with control/no treatment and systemic use of doxycycline, SRP was significantly better at improving (lowering) PI. 6 therapies showed a significantly better effect than SRP (Table 3.43-3.44).

In direct evidence (Figure 3.12) and the fixed-effects model, several therapies appeared to have a better effect than SRP; however, these significant differences were not conserved in the random-effects network model. Of note, results from the fixed-effects model showed “SRP plus SDD rinse” had a worse outcome than SRP. Based on DIC and total residual deviance, the random-effects model seemed to be a better fit (Table 3.45).

TABLE 3.43 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	2.27* (0.56)	—									
3	-4.87* (2.03)	-7.13* (1.94)	—								
4	-3.31* (1.48)	-5.58* (1.36)	1.56 (2.02)	—							
5	0.55 (0.83)	-1.72 (0.90)	5.42* (2.14)	3.86* (1.63)	—						
6	0.24 (1.20)	-2.02 (1.32)	5.11* (2.36)	3.56 (1.90)	-0.31 (1.46)	—					
7	2.98* (1.39)	0.72 (1.47)	7.85* (2.44)	6.30* (2.01)	2.43 (1.61)	2.74 (1.84)	—				
8	-1.44 (1.22)	-3.71* (1.34)	3.43 (2.36)	1.87 (1.92)	-1.99 (1.47)	-1.69 (1.71)	-4.43* (1.85)	—			
9	0.00 (0.83)	-2.27* (0.94)	4.86* (2.16)	3.31 (1.66)	-0.56 (1.16)	-0.25 (1.45)	-2.99 (1.62)	1.44 (1.48)	—		
10	-0.11 (0.59)	-2.37* (0.77)	4.76* (2.09)	3.20* (1.57)	-0.66 (1.01)	-0.35 (1.33)	-3.09* (1.25)	1.34 (1.35)	-0.10 (1.01)	—	
11	0.41 (1.21)	-1.85 (1.33)	5.28* (2.36)	3.73 (1.91)	-0.14 (1.46)	0.17 (1.21)	-2.57 (1.84)	1.86 (1.70)	0.42 (1.46)	0.52 (1.35)	—
12	-0.09 (1.11)	-2.36 (1.23)	4.78* (2.30)	3.22 (1.84)	-0.64 (1.38)	-0.33 (1.63)	-3.07 (1.67)	1.35 (1.64)	-0.08 (1.38)	0.02 (1.11)	-0.50 (1.63)
13	0.86 (0.81)	-1.40 (0.78)	5.73* (2.10)	4.18* (1.57)	0.31 (1.12)	0.62 (1.45)	-2.12 (1.59)	2.31 (1.46)	0.87 (0.98)	0.97 (0.98)	0.45 (1.45)
14	1.54	-0.72	6.41*	4.86*	0.99	1.30	-1.44	2.99	1.55	1.65	1.13

	(1.19)	(1.12)	(2.24)	(1.76)	(1.41)	(1.70)	(1.81)	(1.71)	(1.36)	(1.31)	(1.70)
15	-3.89* (1.39)	-6.15* (1.27)	0.98 (2.33)	-0.57 (1.86)	-4.44* (1.55)	-4.13* (1.83)	-6.87* (1.94)	-2.44 (1.84)	-3.88* (1.59)	-3.78* (1.49)	-4.30* (1.83)
16	0.51 (1.07)	-1.76 (1.13)	5.38* (2.25)	3.82* (1.77)	-0.04 (1.33)	0.27 (1.60)	-2.48 (1.74)	1.95 (1.63)	0.51 (1.11)	0.62 (1.21)	0.09 (1.62)
17	0.71 (1.48)	-1.56 (1.46)	5.58* (2.41)	4.02* (1.99)	0.16 (1.66)	0.47 (1.90)	-2.28 (2.02)	2.15 (1.92)	0.71 (1.57)	0.82 (1.58)	0.29 (1.90)
18	1.00 (1.46)	-1.27 (1.44)	5.87* (2.42)	4.31* (1.98)	0.45 (1.65)	0.76 (1.89)	-1.98 (2.01)	2.44 (1.90)	1.01 (1.55)	1.11 (1.56)	0.59 (1.89)
19	0.72 (1.46)	-1.54 (1.45)	5.59* (2.43)	4.03* (1.98)	0.17 (1.65)	0.48 (1.88)	-2.26 (2.00)	2.16 (1.91)	0.73 (1.56)	0.83 (1.56)	0.31 (1.89)
20	1.69 (1.94)	-0.57 (1.92)	6.56* (2.72)	5.00* (2.35)	1.14 (2.09)	1.45 (2.27)	-1.29 (2.38)	3.13 (2.31)	1.70 (2.01)	1.80 (2.02)	1.28 (2.28)
21	0.37 (1.32)	-1.90 (1.20)	5.24* (2.28)	3.68* (1.81)	-0.18 (1.50)	0.13 (1.77)	-2.62 (1.89)	1.81 (1.78)	0.37 (1.52)	0.48 (1.42)	-0.04 (1.79)
22	-5.45* (1.60)	-7.71* (1.49)	-0.58 (1.24)	-2.13 (1.61)	-6.00* (1.75)	-5.69* (2.00)	-8.43* (2.11)	-4.00 (2.02)	-5.44* (1.77)	-5.34* (1.69)	-5.86* (2.01)
23	-5.16* (1.29)	-7.42* (1.40)	-0.29 (2.40)	-1.85 (1.96)	-5.71* (1.53)	-5.40* (1.76)	-8.14* (1.89)	-3.72* (1.77)	-5.15* (1.53)	-5.05* (1.42)	-5.57* (1.77)
24	-0.31 (1.24)	-2.58 (1.36)	4.55 (2.38)	3.00 (1.92)	-0.86 (1.48)	-0.56 (1.73)	-3.30 (1.85)	1.13 (1.73)	-0.31 (1.49)	-0.21 (1.37)	-0.73 (1.74)
25	-0.82 (1.21)	-3.08* (1.33)	4.05 (2.34)	2.50 (1.90)	-1.37 (1.47)	-1.06 (1.71)	-3.80* (1.83)	0.63 (1.71)	-0.81 (1.47)	-0.71 (1.35)	-1.23 (1.70)
26	0.67 (1.21)	-1.60 (1.33)	5.54* (2.34)	3.98* (1.90)	0.12 (1.46)	0.43 (1.70)	-2.32 (1.84)	2.11 (1.72)	0.67 (1.47)	0.78 (1.34)	0.25 (1.71)
27	-0.15 (1.22)	-2.41 (1.34)	4.72 (2.36)	3.17 (1.92)	-0.70 (1.47)	-0.39 (1.71)	-3.13 (1.84)	1.30 (1.73)	-0.14 (1.46)	-0.04 (1.35)	-0.56 (1.72)
28	-0.76 (1.22)	-3.03* (1.34)	4.10 (2.37)	2.55 (1.91)	-1.31 (1.47)	-1.01 (1.71)	-3.75 (1.85)	0.68 (1.72)	-0.76 (1.47)	-0.66 (1.35)	-1.18 (1.73)
29	-0.11 (1.24)	-2.38 (1.35)	4.76* (2.37)	3.20 (1.92)	-0.66 (1.49)	-0.35 (1.72)	-3.09 (1.85)	1.33 (1.74)	-0.11 (1.49)	0.00 (1.37)	-0.52 (1.74)
30	0.26 (0.88)	-2.01 (1.03)	5.12* (2.19)	3.57* (1.72)	-0.30 (1.21)	0.01 (1.48)	-2.73 (1.64)	1.70 (1.50)	0.26 (1.21)	0.36 (1.06)	-0.16 (1.49)
31	2.34 (1.75)	0.07 (1.70)	7.20* (2.59)	5.65* (2.19)	1.79 (1.91)	2.09 (2.13)	-0.65 (2.23)	3.78 (2.14)	2.34 (1.87)	2.44 (1.83)	1.92 (2.13)
32	1.29 (1.02)	-0.97 (0.93)	6.16* (2.16)	4.61* (1.66)	0.74 (1.26)	1.05 (1.58)	-1.69 (1.71)	2.74 (1.60)	1.30 (1.22)	1.40 (1.15)	0.88 (1.58)
33	-5.66* (2.02)	-7.93* (1.93)	-0.80 (1.73)	-2.35 (2.02)	-6.22* (2.13)	-5.91* (2.35)	-8.65* (2.43)	-4.22 (2.36)	-5.66* (2.15)	-5.56* (2.08)	-6.08* (2.35)
Treatment	12	13	14	15	16	17	18	19	20	21	22
12	—										
13	0.95 (1.37)	—									
14	1.63 (1.61)	0.68 (1.11)	—								
15	-3.80* (1.77)	-4.75* (1.49)	-5.43* (1.69)	—							
16	0.60 (1.53)	-0.35 (1.10)	-1.04* (1.48)	4.39* (1.71)	—						
17	0.80 (1.84)	-0.15 (1.24)	-0.84 (1.66)	4.59* (1.93)	0.20 (1.66)	—					
18	1.09 (1.83)	0.14 (1.22)	-0.54 (1.65)	4.89* (1.91)	0.49 (1.63)	0.29 (1.74)	—				
19	0.81 (1.82)	-0.14 (1.21)	-0.82 (1.63)	4.61* (1.92)	0.21 (1.64)	0.01 (1.74)	-0.28 (1.73)	—			
20	1.78 (2.24)	0.83 (1.76)	0.15 (2.09)	5.58* (2.30)	1.18 (2.07)	0.98 (1.25)	0.69 (2.13)	0.97 (2.15)	—		
21	0.46 (1.71)	-0.49 (1.42)	-1.18 (1.63)	4.25* (1.75)	-0.14 (1.64)	-0.34 (1.89)	-0.63 (1.87)	-0.35 (1.87)	-1.32 (2.27)	—	
22	-5.36* (1.95)	-6.31* (1.69)	-6.99* (1.87)	-1.56 (1.96)	-5.95* (1.88)	-6.15* (2.09)	-6.45* (2.08)	-6.17* (2.09)	-7.14* (2.44)	-5.81* (1.92)	—
23	-5.07* (1.68)	-6.02* (1.52)	-6.70* (1.75)	-1.27 (1.89)	-5.67* (1.68)	-5.87* (1.96)	-6.16* (1.94)	-5.88* (1.94)	-6.85* (2.33)	-5.53* (1.84)	0.29 (2.05)

24	-0.22 (1.66)	-1.18 (1.47)	-1.86 (1.71)	3.57 (1.86)	-0.82 (1.64)	-1.02 (1.92)	-1.31 (1.92)	-1.04 (1.90)	-2.01 (2.29)	-0.68 (1.80)	5.13* (2.04)
25	-0.73 (1.64)	-1.68 (1.46)	-2.36 (1.70)	3.07 (1.84)	-1.32 (1.62)	-1.52 (1.91)	-1.82 (1.90)	-1.54 (1.89)	-2.51 (2.28)	-1.19 (1.78)	4.63* (1.99)
26	0.76 (1.63)	-0.20 (1.46)	-0.88 (1.70)	4.55* (1.85)	0.16 (1.62)	-0.04 (1.91)	-0.33 (1.90)	-0.05 (1.90)	-1.02 (2.29)	0.30 (1.79)	6.11* (1.99)
27	-0.06 (1.64)	-1.01 (1.46)	-1.69 (1.70)	3.74* (1.85)	-0.65 (1.61)	-0.85 (1.91)	-1.15 (1.90)	-0.87 (1.90)	-1.84 (2.29)	-0.51 (1.80)	5.30* (2.02)
28	-0.67 (1.64)	-1.63 (1.46)	-2.31 (1.70)	3.12 (1.85)	-1.27 (1.61)	-1.47 (1.92)	-1.76 (1.89)	-1.49 (1.90)	-2.45 (2.29)	-1.13 (1.80)	4.68* (2.02)
29	-0.02 (1.66)	-0.97 (1.47)	-1.65 (1.71)	3.78* (1.85)	-0.62 (1.63)	-0.82 (1.92)	-1.11 (1.91)	-0.83 (1.91)	-1.80 (2.30)	-0.48 (1.79)	5.34* (2.02)
30	0.34 (1.41)	-0.61 (1.19)	-1.29 (1.47)	4.14* (1.64)	-0.25 (1.38)	-0.45 (1.72)	-0.74 (1.70)	-0.47 (1.70)	-1.44 (2.13)	-0.11 (1.58)	5.70* (1.82)
31	2.43 (2.06)	1.47 (1.70)	0.79 (1.27)	6.22* (2.11)	1.83 (1.96)	1.63 (2.10)	1.34 (2.09)	1.61 (2.07)	0.64 (2.44)	1.97 (2.07)	7.78* (2.28)
32	1.38 (1.51)	0.43 (0.94)	-0.25 (1.34)	5.18* (1.57)	0.78 (1.35)	0.58 (1.55)	0.29 (1.55)	0.57 (1.54)	-0.40 (1.99)	0.92 (1.51)	6.74* (1.77)
33	-5.58* (2.31)	-6.53* (2.09)	-7.21* (2.23)	-1.78 (2.31)	-6.17* (2.24)	-6.37* (2.42)	-6.67* (2.41)	-6.39* (2.43)	-7.36* (2.72)	-6.03* (2.28)	-0.22 (1.22)
Treatment	23	24	25	26	27	28	29	30	31	32	33
23	—										
24	4.85* (1.78)	—									
25	4.34* (1.77)	-0.50 (1.72)	—								
26	5.83* (1.76)	0.98 (1.73)	1.48 (1.71)	—							
27	5.01* (1.78)	0.17 (1.74)	0.67 (1.70)	-0.81 (1.72)	—						
28	4.40* (1.78)	-0.45 (1.73)	0.05 (1.71)	-1.43 (1.72)	-0.62 (1.72)	—					
29	5.05* (1.79)	0.20 (1.76)	0.71 (1.72)	-0.78 (1.73)	0.04 (1.73)	0.65 (1.73)	—				
30	5.41* (1.57)	0.57 (1.53)	1.07 (1.49)	-0.41 (1.49)	0.40 (1.50)	1.02 (1.50)	0.37 (1.51)	—			
31	7.49* (2.17)	2.65 (2.13)	3.15 (2.14)	1.67 (2.13)	2.48 (2.13)	3.10 (2.13)	2.45 (2.13)	2.08 (1.95)	—		
32	6.45* (1.64)	1.61 (1.60)	2.11 (1.58)	0.62 (1.59)	1.44 (1.59)	2.06 (1.59)	1.40 (1.59)	1.04 (1.34)	-1.04 (1.86)	—	
33	-0.51 (2.40)	-5.35* (2.38)	-4.85* (2.34)	-6.33* (2.35)	-5.52* (2.36)	-4.90* (2.35)	-5.55* (2.36)	-5.92* (2.19)	-8.00* (2.58)	-6.96* (2.15)	—

* Statistically significant

**Legend:

- | | | |
|---|---|---|
| 1. SRP | 12. SRP + aPDT | 23. SRP + EO-based rinse |
| 2. Control/no treatment | 13. SRP + intensive maintenance | 24. SRP + SMV gel |
| 3. Intensive OHI | 14. SRP + non-intensive maintenance | 25. SRP + CLM gel |
| 4. CHX rinse | 15. OHI+ SRP+ intensive maintenance | 26. SRP + SZ gel |
| 5. Supragingival cleaning | 16. SRP + SDD + intensive maintenance | 27. SRP + AV gel |
| 6. Supragingival cleaning + AZM | 17. SRP + Doxy+ intensive maintenance | 28. SRP + AZM gel |
| 7. Doxy | 18. SRP + AMX+ intensive maintenance | 29. SRP + ALN gel |
| 8. SRP + powered subgingival water irrigation | 19. SRP + MTZ + AMX + intensive maintenance | 30. SRP + TET (topical) |
| 9. SRP + SDD | 20. SRP+ Doxy+ aPDT + intensive maintenance | 31. SRP + TET (topical) + non-intensive maintenance |
| 10. SRP + Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin | 32. SRP + CHX rinse + intensive maintenance |
| 11. SRP + AZM | 22. SRP + CHX rinse | 33. SRP + CHX rinse + Doxy |

**TABLE 3.44 PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

T**	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	26	27	28	29	30	31	32	33
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T: treatment

**Legend:

- | | | |
|--|---|---|
| 12. SRP | 12. SRP + aPDT | 23. SRP + EO-based rinse |
| 13. Control/no treatment | 13. SRP + intensive maintenance | 24. SRP + SMV gel |
| 14. Intensive OHI | 14. SRP + non-intensive maintenance | 25. SRP + CLM gel |
| 15. CHX rinse | 15. OHI+ SRP+ intensive maintenance | 26. SRP + SZ gel |
| 16. Supragingival cleaning | 16. SRP + SDD + intensive maintenance | 27. SRP + AV gel |
| 17. Supragingival cleaning + AZM | 17. SRP + Doxy+ intensive maintenance | 28. SRP + AZM gel |
| 18. Doxy | 18. SRP + AMX+ intensive maintenance | 29. SRP + ALN gel |
| 19. SRP + powered subgingival water irrigation | 19. SRP + MTZ + AMX + intensive maintenance | 30. SRP + TET (topical) |
| 20. SRP + SDD | 20. SRP+ Doxy+ aPDT + intensive maintenance | 31. SRP + TET (topical) + non-intensive maintenance |
| 21. SRP + Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin | 32. SRP + CHX rinse + intensive maintenance |
| 22. SRP + AZM | 22. SRP + CHX rinse | 33. SRP + CHX rinse + Doxy |

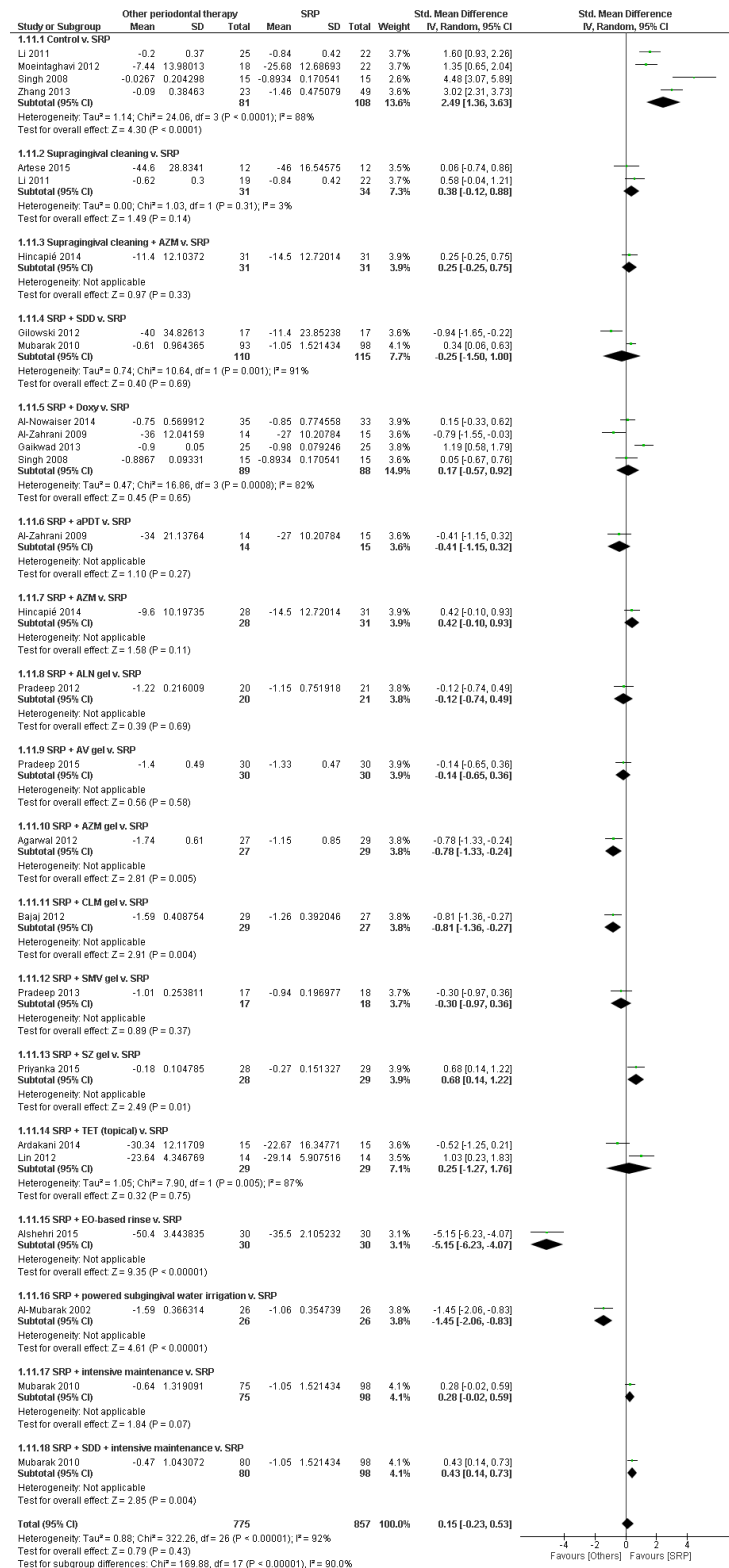
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.45 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR PI AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	2.49* (1.36 to 3.63)	4	88%	2.27 (1.19 to 3.43)	1.70* (1.41 to 1.99)
Supragingival cleaning	SRP	0.38 (-0.12 to 0.88)	2	3%	0.55 (-1.10 to 2.20)	0.43 (-0.03 to 0.90)
Supragingival cleaning + AZM	SRP	0.25 (-0.25 to 0.75)	1	NA	0.24 (-2.16 to 2.64)	0.25 (-0.25 to 0.74)
SRP + SDD	SRP	-0.25 (-1.50 to 1.00)	2	91%	0.00 (-1.66 to 1.63)	0.27* (0.01 to 0.53)
SRP + Doxy	SRP	0.17 (-0.57 to 0.92)	4	82%	-0.11 (-1.31 to 1.04)	0.16 (-0.14 to 0.45)
SRP + aPDT	SRP	-0.41 (-1.15 to 0.32)	1	NA	-0.09 (-2.31 to 2.10)	0.03 (-0.62 to 0.67)
SRP + AZM	SRP	0.42 (-0.10 to 0.93)	1	NA	0.41 (-2.01 to 2.84)	0.42 (-0.09 to 0.93)
SRP + ALN gel	SRP	-0.12 (-0.74 to 0.49)	1	NA	-0.11 (-2.61 to 2.37)	-0.13 (-0.73 to 0.47)
SRP + AV gel	SRP	-0.14 (-0.65 to 0.36)	1	NA	-0.15 (-2.56 to 2.28)	-0.14 (-0.65 to 0.36)
SRP + AZM gel	SRP	-0.78* (-1.33 to -0.24)	1	NA	-0.76 (-3.16 to 1.69)	-0.78* (-1.32 to -0.24)
SRP + CLM gel	SRP	-0.81* (-1.36 to -0.27)	1	NA	-0.82 (-3.21 to 1.60)	-0.81* (-1.34 to -0.28)
SRP + SMV gel	SRP	-0.30 (-0.97 to 0.36)	1	NA	-0.31 (-2.78 to 2.15)	-0.30 (-0.96 to 0.34)
SRP + SZ gel	SRP	0.68* (0.14 to 1.22)	1	NA	0.67 (-1.76 to 3.08)	0.68* (0.15 to 1.20)
SRP + TET (topical)	SRP	0.25 (-1.27 to 1.76)	2	87%	0.26 (-1.49 to 2.04)	0.19 (-0.33 to 0.72)
SRP + EO-based rinse	SRP	-5.15* (-6.23 to -4.07)	1	NA	-5.16* (-7.72 to -2.58)	-5.15* (-6.19 to -4.13)
SRP + powered subgingival water irrigation	SRP	-1.45* (-2.06 to -0.83)	1	NA	-1.44 (-3.86 to 1.01)	-1.45* (-2.05 to -0.84)
SRP + intensive maintenance	SRP	0.28 (-0.02 to 0.59)	1	NA	0.86 (-0.74 to 2.50)	0.48* (0.22 to 0.74)
SRP + SDD + intensive maintenance	SRP	0.43* (0.14 to 0.73)	1	NA	0.51 (-1.62 to 2.64)	0.46* (0.18 to 0.75)
DIC					63.367	128.982
Total residual deviance (Unconstrained data points)					43.89 (78 points)	119.5 (78 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.12 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON PI AT END OF STUDY



3.2.7 GINGIVAL INDEX (GI)

3 months

Fifteen trials have reported the outcome of GI. The evidence network for GI at 3 months included 13 trials, 1404 participants and 12 treatments providing 17 comparisons based on 11 trials with 2 arms and 2 trials with 3 arms (Figure 3.13). Two trials were not included in this network for either lacking data for 3 months (Koromantzou 2011/2012/2014) or not being connected to the network (Skaleric 2004). There was no evidence of inconsistency in the network (Figure A8.31).

At 3 months, SRP showed a significantly better effect than “SRP plus CHX rinse” and control/no treatment in improving (lowering) GI. Two treatments were significantly better than SRP (Table 3.46-3.47). Direct estimates (Figure 3.14) were congruent with mixed estimates with only one exception (“SRP plus powered subgingival water irrigation”). Based on DIC and total residual deviance, the random-effects model seemed to be a better fit (Table 3.48).

FIGURE 3.13 EVIDENCE NETWORK FOR GI AT 3 MONTHS

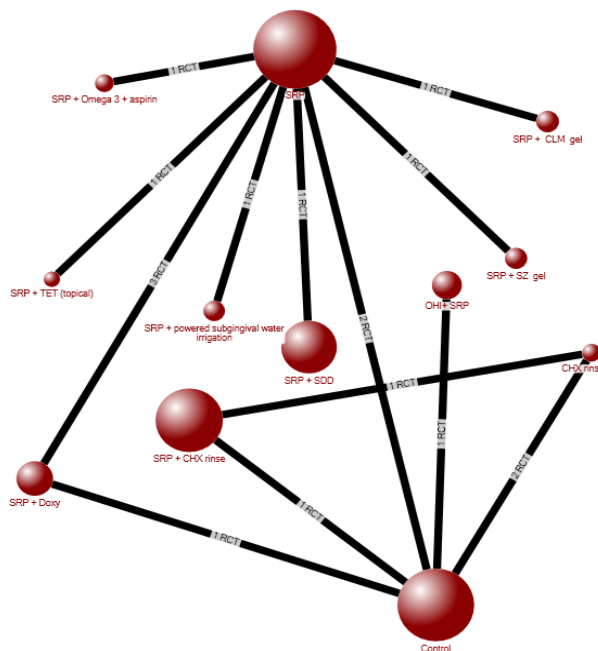


TABLE 3.46 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	3.08* (0.74)	—										
3	-1.02 (1.26)	-4.10* (1.02)	—									
4	0.12 (0.97)	-2.96* (1.23)	1.14 (1.60)	—								
5	0.11 (0.56)	-2.97* (0.84)	1.13 (1.33)	-0.01 (1.12)	—							
6	-2.87* (1.05)	-5.95* (1.28)	-1.85 (1.65)	-2.99* (1.44)	-2.98* (1.19)	—						
7	-0.66 (1.01)	-3.73* (1.24)	0.36 (1.60)	-0.77 (1.41)	-0.77 (1.15)	2.22 (1.47)	—					
8	1.73 (1.20)	-1.35 (0.96)	2.75 (1.39)	1.62 (1.54)	1.62 (1.26)	4.61* (1.59)	2.39 (1.55)	—				
9	2.44* (1.03)	-0.64 (0.71)	3.46* (1.23)	2.32 (1.43)	2.33* (1.09)	5.31* (1.47)	3.09* (1.42)	0.71 (0.97)	—			
10	-2.33* (1.02)	-5.40* (1.27)	-1.31 (1.62)	-2.44 (1.40)	-2.44* (1.16)	0.55 (1.48)	-1.67 (1.44)	-4.06* (1.58)	-4.76* (1.46)	—		
11	-0.53 (0.99)	-3.61* (1.24)	0.49 (1.60)	-0.65 (1.37)	-0.64 (1.13)	2.34 (1.45)	0.12 (1.42)	-2.27 (1.57)	-2.97* (1.44)	1.79 (1.42)	—	
12	0.51 (1.04)	-2.57* (1.27)	1.53 (1.63)	0.39 (1.43)	0.40 (1.17)	3.38* (1.48)	1.16 (1.44)	-1.23 (1.58)	-1.93 (1.45)	2.83 (1.45)	1.04 (1.43)	—

* Statistically significant

**Legend:

- | | | |
|-------------------------|---|-------------------------|
| 1. SRP | 5. SRP + Doxy | 9. SRP + CHX rinse |
| 2. Control/no treatment | 6. SRP + Omega 3 + aspirin | 10. SRP + SZ gel |
| 3. OHI + SRP | 7. SRP + powered subgingival water irrigation | 11. SRP + CLM gel |
| 4. SRP + SDD | 8. CHX rinse | 12. SRP + TET (topical) |

TABLE 3.47 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS (RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)

Treatment**	1	2	3	4	5	6	7	8	9	10	11	12
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												

**Legend:

- | | | |
|-------------------------|---|-------------------------|
| 1. SRP | 5. SRP + Doxy | 9. SRP + CHX rinse |
| 2. Control/no treatment | 6. SRP + Omega 3 + aspirin | 10. SRP + SZ gel |
| 3. OHI + SRP | 7. SRP + powered subgingival water irrigation | 11. SRP + CLM gel |
| 4. SRP + SDD | 8. CHX rinse | 12. SRP + TET (topical) |

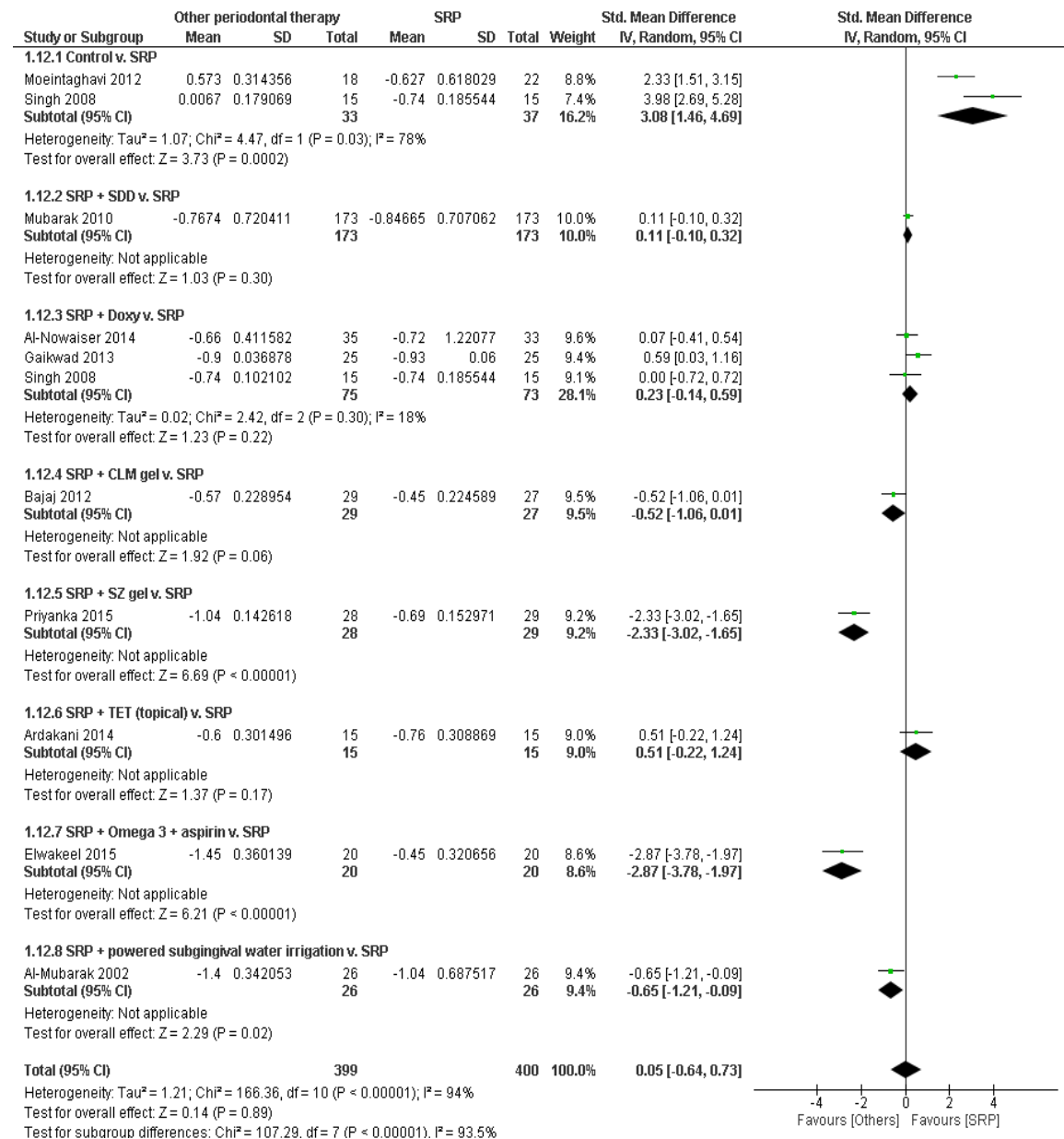
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.48 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR GI AT 3 MONTHS

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	3.08* (1.46 to 4.69)	2	78%	3.08* (1.65 to 4.61)	2.90* (2.27 to 3.55)
SRP + SDD	SRP	0.11 (-0.10 to 0.32)	1	NA	0.12 (-1.89 to 2.14)	0.11 (-0.10 to 0.32)
SRP + Doxy	SRP	0.23 (-0.14 to 0.59)	3	18%	0.11 (-1.09 to 1.21)	0.17 (-0.14 to 0.49)
SRP + CLM gel	SRP	-0.52 (-1.06 to 0.01)	1	NA	-0.53 (-2.58 to 1.50)	-0.52 (-1.05 to 0.01)
SRP + SZ gel	SRP	-2.33* (-3.02 to -1.65)	1	NA	-2.33* (-4.42 to -0.29)	-2.34* (-2.99 to -1.67)
SRP + TET (topical)	SRP	0.51 (-0.22 to 1.24)	1	NA	0.51 (-1.57 to 2.61)	0.50 (-0.21 to 1.21)
SRP + Omega 3 + aspirin	SRP	-2.87* (-3.78 to -1.97)	1	NA	-2.87* (-4.93 to -0.75)	-2.87* (-3.74 to -2.02)
SRP + powered subgingival water irrigation	SRP	-0.65* (-1.21 to -0.09)	1	NA	-0.66 (-2.71 to 1.33)	-0.65* (-1.20 to -0.11)
DIC					21.047	23.836
Total residual deviance (Unconstrained data points)					16.16 (28 points)	22.54 (28 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

FIGURE 3.14 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON GI AT 3 MONTHS



End of study

The evidence network for GI by the end of study included 14 trials with a total of 1464 participants. Overall, 16 treatments were compared, providing 23 comparisons based on 11 trials with 2 arms, 2 trials with 3 arms and 1 trial with 4 arms. One trial (Skaleric 2004) that had reported GI was not included for not being connected to the network. There was no evidence of inconsistency in the network (Figure A8.32).

Results showed that, compared to control/no treatment, SRP had a significant effect in improving (lowering) the GI score. There were no differences between SRP and other periodontal therapies (Table 3.49-3.50). Estimates from direct evidence (Figure 3.15) and the fixed-effects model suggested several treatments to be better than SRP; however, these differences were not conserved in the random-effects model that incorporated indirect evidence. Based on DIC and total residual deviance, the random-effects model was considered to be a better fit (Table 3.51).

**TABLE 3.49 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY
(RANDOM-EFFECTS NMA; MEAN±SD)**

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	3.15* (1.00)	—								
3	1.63 (1.73)	-1.52 (1.41)	—							
4	1.72 (2.00)	-1.42 (2.24)	0.09 (2.65)	—						
5	-0.65 (1.45)	-3.80* (1.76)	-2.29 (2.26)	-2.38 (2.49)	—					
6	2.17 (1.71)	-0.98 (1.40)	0.54 (1.43)	0.44 (2.63)	2.82 (2.24)	—				
7	0.39 (1.41)	-2.76 (1.74)	-1.24 (2.23)	-1.34 (2.01)	1.04 (2.05)	-1.78 (2.21)	—			
8	0.09 (0.80)	-3.06* (1.14)	-1.54 (1.81)	-1.63 (2.14)	0.74 (1.65)	-2.08 (1.80)	-0.30 (1.62)	—		
9	-2.32 (1.44)	-5.47* (1.75)	-3.95 (2.26)	-4.05 (2.46)	-1.67 (2.05)	-4.49 (2.25)	-2.71 (2.03)	-2.41 (1.64)	—	
10	0.28 (1.39)	-2.87 (1.72)	-1.35 (2.21)	-1.45 (1.42)	0.93 (2.01)	-1.89 (2.20)	-0.11 (1.40)	0.19 (1.60)	2.60 (2.00)	—
11	-0.92 (1.74)	-4.07* (1.42)	-2.55 (1.99)	-2.65 (2.67)	-0.27 (2.25)	-3.09 (2.00)	-1.31 (2.27)	-1.01 (1.83)	1.40 (2.25)	-1.20 (2.25)
12	2.76 (1.71)	-0.39 (1.39)	1.13 (1.97)	1.03 (2.62)	3.41 (2.24)	0.59 (1.98)	2.37 (2.22)	2.67 (1.78)	5.08* (2.24)	2.48 (2.20)
13	0.49 (1.40)	-2.66 (1.72)	-1.14 (2.23)	-1.23 (1.99)	1.14 (2.02)	-1.68 (2.21)	0.10 (1.38)	0.40 (1.61)	2.81 (2.00)	0.21 (1.39)
14	-2.57 (1.44)	-5.72* (1.76)	-4.20 (2.23)	-4.29 (2.49)	-1.92 (2.06)	-4.74* (2.24)	-2.96 (2.04)	-2.66 (1.66)	-0.25 (2.05)	-2.85 (2.03)
15	-1.25 (1.44)	-4.40* (1.76)	-2.88 (2.26)	-2.98 (2.48)	-0.60 (2.04)	-3.42 (2.23)	-1.64 (2.04)	-1.34 (1.64)	1.07 (2.03)	-1.53 (2.03)
16	0.53 (1.44)	-2.62 (1.75)	-1.11 (2.26)	-1.20 (2.47)	1.18 (2.03)	-1.64 (2.24)	0.14 (2.02)	0.44 (1.64)	2.85 (2.05)	0.25 (2.00)
Treatment	11	12	13	14	15	16				
11	—									
12	3.68 (1.98)	—								
13	1.41 (2.25)	-2.27 (2.21)	—							
14	-1.65 (2.26)	-5.33* (2.25)	-3.06 (2.01)	—						
15	-0.33 (2.28)	-4.01 (2.24)	-1.74 (2.01)	1.32 (2.02)	—					
16	1.45 (2.26)	-2.23 (2.24)	0.04 (2.01)	3.10 (2.02)	1.78 (2.03)	—				

* Statistically significant

**Legend:

- | | | |
|---|---|---------------------------------------|
| 1. SRP | 7. SRP + SDD | 13. SRP + SDD + intensive maintenance |
| 2. Control/no treatment | 8. SRP + Doxy | 14. SRP + SZ gel |
| 3. CHX rinse | 9. SRP + Omega 3 + aspirin | 15. SRP + CLM gel |
| 4. Supragingival cleaning | 10. SRP + intensive maintenance | 16. SRP + TET (topical) |
| 5. SRP + powered subgingival water irrigation | 11. OHI+ SRP+ intensive maintenance | |
| 6. SRP + CHX rinse | 12. SRP + CHX rinse + intensive maintenance | |

**TABLE 3.50 GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY
(RANDOM-EFFECTS NMA; VISUAL REPRESENTATION)**

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

**Legend:

- | | | |
|---|---|---------------------------------------|
| 1. SRP | 7. SRP + SDD | 13. SRP + SDD + intensive maintenance |
| 2. Control/no treatment | 8. SRP + Doxy | 14. SRP + SZ gel |
| 3. CHX rinse | 9. SRP + Omega 3 + aspirin | 15. SRP + CLM gel |
| 4. Supragingival cleaning | 10. SRP + intensive maintenance | 16. SRP + TET (topical) |
| 5. SRP + powered subgingival water irrigation | 11. OHI+ SRP+ intensive maintenance | |
| 6. SRP + CHX rinse | 12. SRP + CHX rinse + intensive maintenance | |

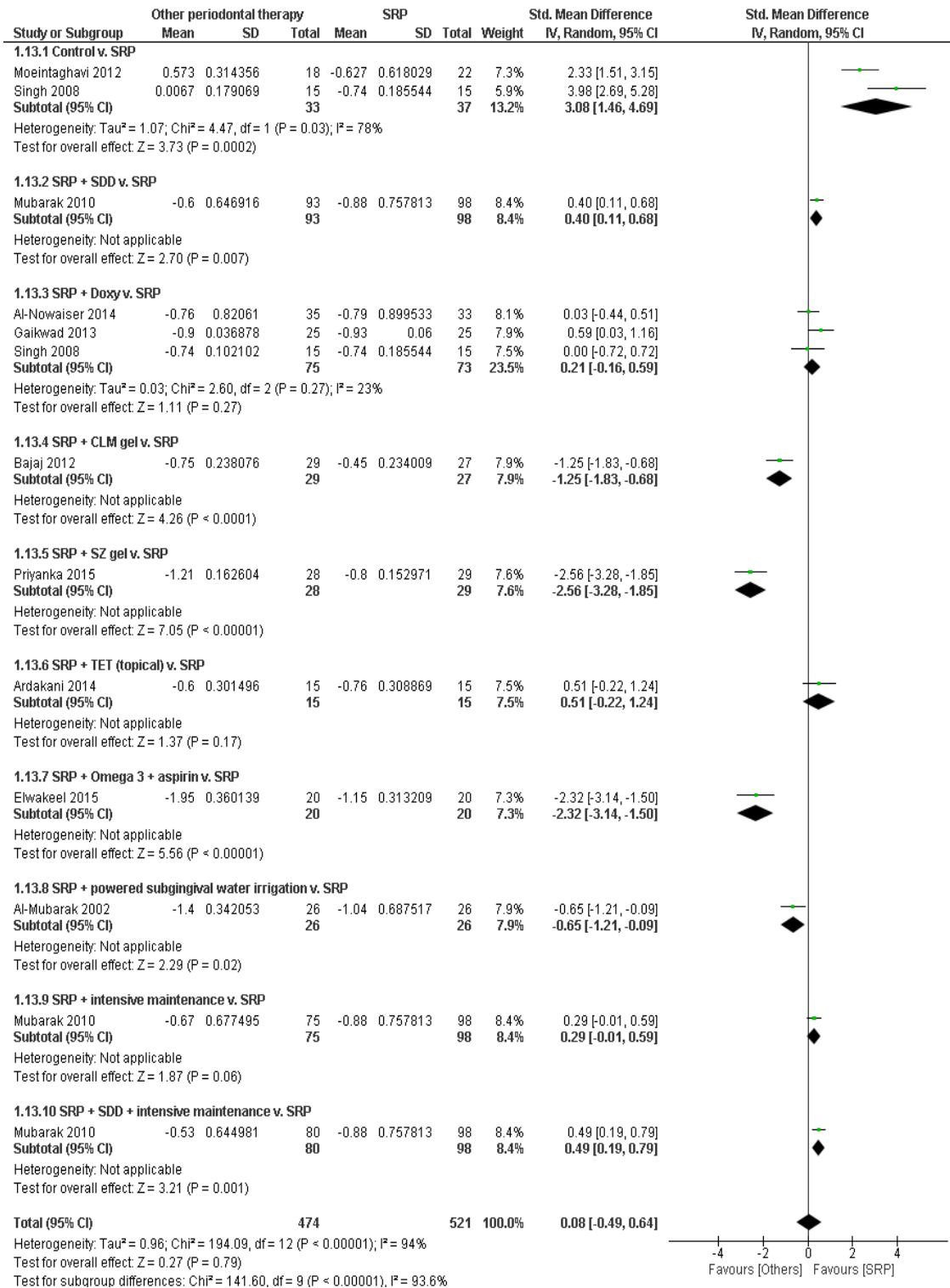
Green cells indicate a statistically significant improvement of HbA1c; red cells indicate a statistically worse outcome, and grey cells indicate no statistical difference between treatments. If printed as black and white, red cells appear black; green cells appear dark grey.

TABLE 3.51 COMPARISON OF DIRECT AND INDIRECT EVIDENCE FOR GI AT END OF STUDY

Comparison		Direct evidence (RE model)			Direct + indirect evidence (derived from NMA)	
		MD (95% CI)	No. of studies	I^2 , %	RE model MD (95% CrI)	FE model MD (95% CrI)
Control/no treatment	SRP	3.08* (1.46 to 4.69)	2	78%	3.15* (1.25 to 5.29)	2.89* (2.22 to 3.55)
SRP + SDD	SRP	0.40* (0.11 to 0.68)	1	NA	0.39 (-2.58 to 3.29)	0.40* (0.11 to 0.68)
SRP + Doxy	SRP	0.21 (-0.16 to 0.59)	3	23%	0.09 (-1.63 to 1.73)	0.16 (-0.16 to 0.48)
SRP + CLM gel	SRP	-1.25* (-1.83 to -0.68)	1	NA	-1.25 (-4.29 to 1.79)	-1.26* (-1.82 to -0.69)
SRP + SZ gel	SRP	-2.56* (-3.28 to -1.85)	1	NA	-2.57 (-5.56 to 0.42)	-2.57* (-3.26 to -1.88)
SRP + TET (topical)	SRP	0.51 (-0.22 to 1.24)	1	NA	0.53 (-2.53 to 3.59)	0.51 (-0.20 to 1.21)
SRP + Omega 3 + aspirin	SRP	-2.32* (-3.14 to -1.50)	1	NA	-2.32 (-5.34 to 0.66)	-2.32* (-3.11 to -1.54)
SRP + powered subgingival water irrigation	SRP	-0.65* (-1.21 to -0.09)	1	NA	-0.65 (-3.68 to 2.32)	-0.66* (-1.21 to -0.10)
SRP + intensive maintenance	SRP	0.29 (-0.01 to 0.59)	1	NA	0.28 (-2.75 to 3.16)	0.29 (-0.01 to 0.59)
SRP + SDD + intensive maintenance	SRP	0.49* (0.19 to 0.79)	1	NA	0.49 (-2.49 to 3.42)	0.49* (0.19 to 0.79)
				DIC	22.569	24.823
				Total residual deviance (Unconstrained data points)	18.74 (32 points)	23.83 (32 points)

Note: CI = confidence interval, CrI = credible interval, DIC = deviance information criteria, FE= fixed-effects, NA = not applicable, NMA = network meta-analysis, MD = mean difference, RE= random-effects. * $p < 0.05$.

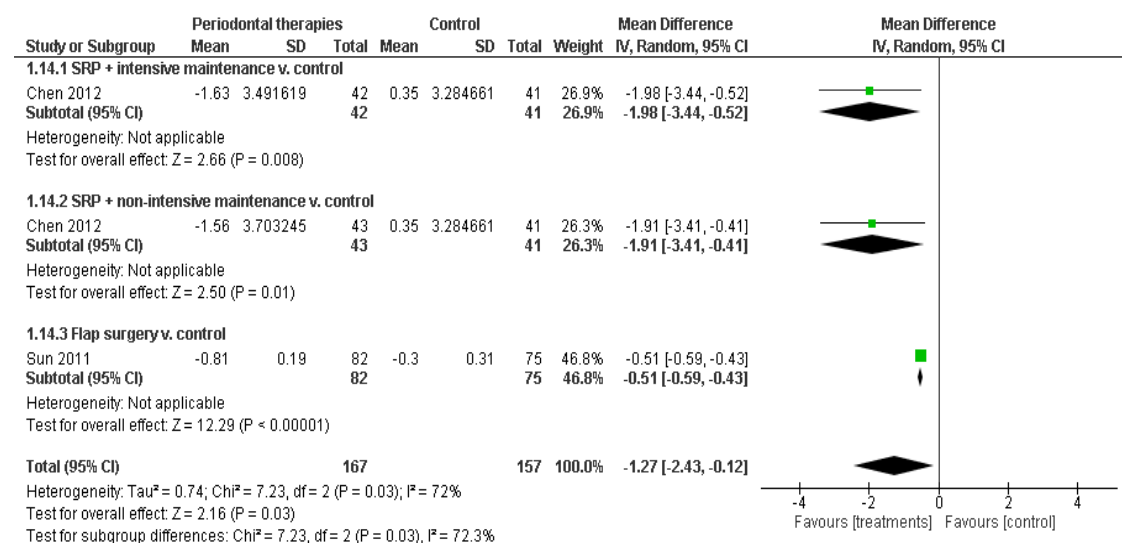
FIGURE 3.15 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON GI AT END OF STUDY



3.2.8 C-REACTIVE PROTEIN (CRP)

Five trials had reported CRP as an outcome and all used the assay of hsCRP. Two trials (Koromantzios 2012; Raman 2014) compared the effect of different periodontal treatments and reported no statistical difference between groups. The other 3 trials (Chen 2012; Sun 2011; Katagiri 2008) assessed the effect of periodontal treatments versus control/no treatment (Figure 3.16). Chen 2012 and Sun 2011 concluded that periodontal treatments could significantly decrease hsCRP. However, Katagiri 2008 reported a non-significant result with no available data in the article.

FIGURE 3.16 DIRECT EVIDENCE FROM PRIMARY STUDIES REPORTING THE EFFECT OF PERIODONTAL THERAPIES ON CRP (VERSUS CONTROL/NO TREATMENT)



3.2.9 GINGIVAL CREVICULAR FLUID (GCF) VOLUME

Two trials (Gilowski 2012; Mendonca 2012) assessed the effect of periodontal treatments on GCF volume. Both reported periodontal treatments could reduce GCF flow but no significant difference was found between different treatment groups. Pairwise meta-analysis could not be undertaken due to lack of data.

3.3 SUBGROUP ANALYSIS

Both sensitivity and subgroup analyses were pre-specified for the primary outcome only (i.e. HbA1c). Results of these analyses were not always consistent with the previous results. In order to further explore these differences, we performed several sensitivity and subgroup analyses for PPD and CAL as well. Because classification of subgroups was based on the baseline mean and 95% confidence interval and was somewhat arbitrary, the findings should be interpreted with caution.

AGE

Except trials that had baseline 95% CI including 65 and cannot be divided into either subgroup, all of the rest of the trials were categorized into the subgroup of less than 65 years.

3 months — Hemoglobin A1C (HbA1c)

This network meta-analysis included 18 trials, 1900 participants and 16 treatments providing 24 comparisons based on 15 trials with 2 arms and 3 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.6).

The results showed no statistically significant difference between any comparisons (Table 3.52). Even SRP showed no significant effect on reducing HbA1c relative to the control/no treatment condition.

TABLE 3.52 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.58 (0.36)	—								
3	0.74 (0.71)	0.17 (0.64)	—							
4	0.78 (0.53)	0.21 (0.64)	0.04 (0.88)	—						
5	0.29 (0.64)	-0.28 (0.74)	-0.45 (0.95)	-0.49 (0.84)	—					
6	-0.21 (0.55)	-0.78 (0.42)	-0.95 (0.77)	-0.99 (0.76)	-0.50 (0.84)	—				
7	-0.17 (0.50)	-0.75 (0.62)	-0.91 (0.87)	-0.95 (0.73)	-0.46 (0.82)	0.04 (0.74)	—			
8	-0.08 (0.29)	-0.65 (0.46)	-0.82 (0.76)	-0.86 (0.60)	-0.37 (0.67)	0.13 (0.62)	0.09 (0.58)	—		
9	0.09 (0.37)	-0.48 (0.51)	-0.65 (0.80)	-0.69 (0.65)	-0.20 (0.52)	0.30 (0.66)	0.26 (0.63)	0.17 (0.43)	—	
10	-0.22 (0.53)	-0.79 (0.63)	-0.96 (0.88)	-1.00 (0.54)	-0.51 (0.84)	-0.01 (0.76)	-0.05 (0.73)	-0.14 (0.60)	-0.31 (0.65)	—
11	0.13 (0.51)	-0.45 (0.61)	-0.61 (0.86)	-0.65 (0.74)	-0.16 (0.82)	0.34 (0.75)	0.30 (0.72)	0.21 (0.59)	0.04 (0.63)	0.35 (0.73)
12	-0.11 (0.33)	-0.69 (0.49)	-0.86 (0.78)	-0.90 (0.63)	-0.41 (0.69)	0.09 (0.64)	0.06 (0.60)	-0.04 (0.44)	-0.21 (0.45)	0.10 (0.62)
13	0.22 (0.53)	-0.36 (0.40)	-0.53 (0.76)	-0.56 (0.75)	-0.07 (0.84)	0.43 (0.58)	0.39 (0.73)	0.30 (0.61)	0.13 (0.65)	0.43 (0.75)
14	0.55 (0.47)	-0.03 (0.38)	-0.20 (0.52)	-0.24 (0.71)	0.26 (0.80)	0.75 (0.57)	0.72 (0.69)	0.62 (0.55)	0.45 (0.60)	0.76 (0.71)
15	0.47 (0.57)	-0.10 (0.45)	-0.27 (0.78)	-0.31 (0.78)	0.18 (0.86)	0.68 (0.61)	0.64 (0.76)	0.55 (0.64)	0.38 (0.68)	0.69 (0.78)
16	0.68 (0.63)	0.10 (0.56)	-0.06 (0.66)	-0.10 (0.82)	0.39 (0.90)	0.89 (0.70)	0.85 (0.80)	0.76 (0.69)	0.59 (0.73)	0.90 (0.82)
Treatment	11	12	13	14	15	16				
11	—									
12	-0.25 (0.60)	—								
13	0.09 (0.74)	0.33 (0.63)	—							
14	0.42 (0.69)	0.66 (0.58)	0.33 (0.55)	—						
15	0.34 (0.76)	0.59 (0.66)	0.25 (0.59)	-0.07 (0.58)	—					
16	0.55 (0.80)	0.80 (0.72)	0.46 (0.69)	0.13 (0.42)	0.21 (0.72)	—				

**Legend:

- | | |
|---|---|
| 1. SRP | 9. SRP + Doxy |
| 2. Control/no treatment | 10. SRP + AZM |
| 3. Intensive OHI | 11. SRP + MTZ + AMX |
| 4. Supragingival cleaning + AZM | 12. SRP + aPDT |
| 5. Doxy | 13. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. OHI + SRP | 14. SRP + CHX rinse |
| 7. SRP + powered subgingival water irrigation | 15. SRP + TET (topical) + intensive maintenance |
| 8. SRP + SDD | 16. SRP + CHX rinse + Doxy |

End of study — Hemoglobin A1C (HbA1c)

The network included 21 trials, 1979 participants and 20 treatments, providing 32 comparisons based on 17 trials with 2 arms, 3 trials with 3 arms and 1 trial with 4 arms. There was no evidence of inconsistency in the network (Figure A8.14).

By the end of study, compared to control/no treatment, SRP showed no significant effect on reducing HbA1c. There were no statistically significant differences between other periodontal treatments with SRP (Table 3.53).

TABLE 3.53 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.65 (0.37)	—								
3	0.63 (0.51)	-0.02 (0.60)	—							
4	0.12 (0.55)	-0.54 (0.66)	-0.51 (0.74)	—						
5	0.28 (0.66)	-0.38 (0.75)	-0.35 (0.82)	0.16 (0.85)	—					
6	-0.15 (0.52)	-0.81 (0.64)	-0.78 (0.73)	-0.27 (0.75)	-0.43 (0.84)	—				
7	-0.09 (0.32)	-0.74 (0.48)	-0.72 (0.56)	-0.21 (0.63)	-0.36 (0.70)	0.07 (0.61)	—			
8	0.10 (0.38)	-0.55 (0.53)	-0.53 (0.63)	-0.02 (0.67)	-0.18 (0.53)	0.25 (0.64)	0.19 (0.44)	—		
9	-0.58 (0.57)	-1.23 (0.68)	-1.21 (0.76)	-0.70 (0.55)	-0.86 (0.87)	-0.43 (0.77)	-0.49 (0.65)	-0.68 (0.68)	—	
10	-0.21 (0.84)	-0.86 (0.92)	-0.84 (0.98)	-0.33 (1.01)	-0.48 (1.08)	-0.05 (0.98)	-0.12 (0.89)	-0.31 (0.92)	0.37 (1.01)	—
11	-0.10 (0.34)	-0.76 (0.50)	-0.73 (0.60)	-0.22 (0.65)	-0.38 (0.71)	0.05 (0.62)	-0.02 (0.46)	-0.20 (0.47)	0.48 (0.66)	0.10 (0.91)
12	-0.17 (0.45)	-0.82 (0.54)	-0.80* (0.41)	-0.29 (0.70)	-0.44 (0.78)	-0.01 (0.69)	-0.08 (0.48)	-0.27 (0.57)	0.41 (0.71)	0.04 (0.94)
13	-0.41 (0.58)	-1.06* (0.44)	-1.04 (0.75)	-0.53 (0.80)	-0.68 (0.87)	-0.25 (0.78)	-0.32 (0.65)	-0.51 (0.69)	0.17 (0.81)	-0.20 (1.02)
14	0.25 (0.50)	-0.40 (0.60)	-0.38 (0.63)	0.13 (0.74)	-0.03 (0.81)	0.41 (0.72)	0.34 (0.50)	0.15 (0.61)	0.83 (0.75)	0.46 (0.97)
15	-0.77 (0.77)	-1.42 (0.83)	-1.40 (0.76)	-0.89 (0.94)	-1.05 (1.00)	-0.61 (0.94)	-0.68 (0.79)	-0.87 (0.85)	-0.19 (0.95)	-0.56 (1.13)
16	0.67 (0.74)	0.02 (0.80)	0.04 (0.72)	0.56 (0.91)	0.40 (0.98)	0.83 (0.91)	0.76 (0.76)	0.57 (0.82)	1.25 (0.92)	0.88 (1.11)
17	-1.23 (0.93)	-1.88 (0.99)	-1.86* (0.92)	-1.35 (1.08)	-1.51 (1.13)	-1.08 (1.08)	-1.14 (0.95)	-1.33 (1.00)	-0.65 (1.09)	-1.02 (1.24)
18	0.29 (0.56)	-0.36 (0.42)	-0.34 (0.74)	0.18 (0.78)	0.02 (0.86)	0.45 (0.76)	0.38 (0.64)	0.19 (0.67)	0.87 (0.80)	0.50 (1.01)
19	0.46 (0.58)	-0.20 (0.45)	-0.17 (0.75)	0.34 (0.80)	0.18 (0.88)	0.61 (0.77)	0.54 (0.66)	0.36 (0.70)	1.03 (0.81)	0.66 (1.02)
20	0.73 (0.51)	0.08 (0.40)	0.10 (0.67)	0.61 (0.75)	0.46 (0.83)	0.89 (0.73)	0.82 (0.59)	0.63 (0.64)	1.31 (0.76)	0.94 (0.98)
Treatment	11	12	13	14	15	16	17	18	19	20
11	—									
12	-0.06 (0.56)	—								
13	-0.30 (0.67)	-0.24 (0.70)	—							
14	0.35	0.42	0.66	—						

	(0.60)	(0.54)	(0.75)							
15	-0.67 (0.84)	-0.60 (0.64)	-0.36 (0.95)	-1.02 (0.83)	—					
16	0.78 (0.82)	0.84 (0.60)	1.08 (0.92)	0.42 (0.81)	1.44 (0.88)	—				
17	-1.13 (0.99)	-1.06 (0.83)	-0.82 (1.08)	-1.48 (0.98)	-0.46 (0.53)	-1.90 (1.02)	—			
18	0.40 (0.65)	0.46 (0.69)	0.70 (0.61)	0.04 (0.74)	1.06 (0.93)	-0.38 (0.90)	1.52 (1.07)	—		
19	0.56 (0.68)	0.62 (0.70)	0.86 (0.63)	0.20 (0.75)	1.22 (0.95)	-0.22 (0.92)	1.69 (1.08)	0.16 (0.62)	—	
20	0.84 (0.61)	0.90 (0.60)	1.14 (0.60)	0.48 (0.69)	1.50 (0.87)	0.06 (0.85)	1.96 (1.02)	0.44 (0.58)	0.28 (0.61)	—

* Statistically significant

**Legend:

- | | | |
|---|---------------------------------------|---|
| 1. SRP | 8. SRP + Doxy | 15. SRP + Doxy+ intensive maintenance |
| 2. Control/no treatment | 9. SRP + AZM | 16. SRP + MTZ + AMX + intensive maintenance |
| 3. Supragingival cleaning | 10. SRP + ALN | 17. SRP+ Doxy+ aPDT + intensive maintenance |
| 4. Supragingival cleaning + AZM | 11. SRP + aPDT | 18. SRP/flap surgery+ Tinidazole + Ampicillin |
| 5. Doxy | 12. SRP + intensive maintenance | 19. SRP + TET (topical) + intensive maintenance |
| 6. SRP + powered subgingival water irrigation | 13. OHI+ SRP+ intensive maintenance | 20. SRP + CHX rinse + intensive maintenance |
| 7. SRP + SDD | 14. SRP + SDD + intensive maintenance | |

3 months — Periodontal pocket depth (PPD)

This network meta-analysis included 21 trials, 1940 participants and 21 treatments providing 25 comparisons based on 19 trials with 2 arms and 2 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.19).

The results showed no statistically significant difference between SRP and control/no treatment. 4 treatments showed a significantly better effect on reducing HbA1c than SRP (Table 3.54).

TABLE 3.54 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.42 (0.29)	—									
3	0.68 (0.45)	0.26 (0.45)	—								
4	-0.1 (0.35)	-0.51 (0.44)	-0.77 (0.56)	—							
5	0.43 (0.49)	0.01 (0.57)	-0.25 (0.67)	0.53 (0.61)	—						
6	-0.4 (0.45)	-0.82* (0.34)	-1.08* (0.58)	-0.31 (0.56)	-0.83 (0.66)	—					
7	-0.07 (0.37)	-0.49 (0.47)	-0.75 (0.58)	0.03 (0.5)	-0.5 (0.62)	0.33 (0.57)	—				
8	-0.1 (0.25)	-0.51 (0.38)	-0.77 (0.51)	0 (0.43)	-0.53 (0.56)	0.31 (0.52)	-0.03 (0.43)	—			
9	0.15 (0.29)	-0.27 (0.41)	-0.53 (0.54)	0.25 (0.45)	-0.28 (0.4)	0.55 (0.53)	0.22 (0.46)	0.24 (0.39)	—		
10	-0.3 (0.35)	-0.71 (0.44)	-0.98* (0.56)	-0.2 (0.34)	-0.73 (0.61)	0.11 (0.56)	-0.23 (0.5)	-0.45 (0.43)	-0.2 (0.46)	—	

11	-0.4 (0.35)	-0.81* (0.44)	-1.07* (0.56)	-0.3 (0.49)	-0.83 (0.6)	0.01 (0.57)	-0.33 (0.51)	-0.3 (0.43)	-0.55 (0.45)	-0.1 (0.49)	—
12	0.14 (0.34)	-0.27 (0.45)	-0.53 (0.57)	0.24 (0.49)	-0.29 (0.52)	0.55 (0.57)	0.21 (0.49)	0.24 (0.41)	0 (0.33)	0.44 (0.49)	0.54 (0.49)
13	-0.93* (0.44)	-1.34* (0.34)	-1.6* (0.57)	-0.83 (0.56)	-1.36* (0.67)	-0.52 (0.48)	-0.85 (0.58)	-0.83 (0.51)	-1.07* (0.54)	-0.63 (0.56)	-0.53 (0.56)
14	0.15 (0.28)	-0.27 (0.28)	-0.53 (0.36)	0.24 (0.45)	-0.28 (0.57)	0.55 (0.45)	0.22 (0.46)	0.24 (0.38)	0 (0.41)	0.45 (0.44)	0.54 (0.44)
15	-1.3* (0.34)	-1.72* (0.44)	-1.98* (0.56)	-1.2* (0.5)	-1.73* (0.6)	-0.9 (0.56)	-1.23* (0.51)	-1.21* (0.42)	-1.45* (0.46)	-1* (0.49)	-0.9* (0.49)
16	-0.73* (0.36)	-1.14* (0.46)	-1.41* (0.57)	-0.63 (0.5)	-1.16* (0.61)	-0.32 (0.57)	-0.66 (0.52)	-0.63 (0.44)	-0.88* (0.47)	-0.43 (0.51)	-0.33 (0.5)
17	-0.28 (0.38)	-0.69 (0.47)	-0.95 (0.59)	-0.18 (0.52)	-0.71 (0.62)	0.13 (0.58)	-0.21 (0.52)	-0.18 (0.46)	-0.43 (0.48)	0.02 (0.52)	0.12 (0.52)
18	-1.01* (0.35)	-1.43* (0.45)	-1.69* (0.57)	-0.92* (0.5)	-1.44* (0.61)	-0.61 (0.57)	-0.94* (0.51)	-0.92* (0.43)	-1.16* (0.46)	-0.71 (0.5)	-0.61 (0.49)
19	0.04 (0.42)	-0.37 (0.5)	-0.63 (0.61)	0.14 (0.54)	-0.38 (0.64)	0.45 (0.6)	0.12 (0.55)	0.14 (0.48)	-0.1 (0.51)	0.34 (0.54)	0.44 (0.54)
20	-0.18 (0.48)	-0.6 (0.38)	-0.86 (0.59)	-0.08 (0.59)	-0.61 (0.68)	0.22 (0.5)	-0.11 (0.6)	-0.08 (0.54)	-0.33 (0.56)	0.12 (0.59)	0.22 (0.59)
21	0.06 (0.45)	-0.36 (0.45)	-0.62 (0.5)	0.15 (0.57)	-0.37 (0.68)	0.46 (0.57)	0.13 (0.57)	0.15 (0.51)	-0.09 (0.55)	0.36 (0.56)	0.46 (0.57)
Treatment	12	13	14	15	16	17	18	19	20	21	
12	—										
13	-1.07* (0.56)	—									
14	0 (0.45)	1.07* (0.44)	—								
15	-1.45* (0.48)	-0.38 (0.56)	-1.45* (0.44)	—							
16	-0.87* (0.5)	0.2 (0.57)	-0.88* (0.46)	0.57 (0.5)	—						
17	-0.42 (0.52)	0.65 (0.58)	-0.42 (0.47)	1.03* (0.51)	0.45 (0.53)	—					
18	-1.16* (0.5)	-0.09 (0.56)	-1.16* (0.45)	0.29 (0.49)	-0.28 (0.5)	-0.74 (0.52)	—				
19	-0.1 (0.54)	0.97 (0.61)	-0.1 (0.5)	1.35* (0.54)	0.77 (0.54)	0.32 (0.56)	1.06* (0.55)	—			
20	-0.32 (0.58)	0.75 (0.5)	-0.33 (0.48)	1.12* (0.58)	0.55 (0.59)	0.1 (0.61)	0.83 (0.58)	-0.23 (0.63)	—		
21	-0.09 (0.57)	0.98* (0.57)	-0.09 (0.35)	1.36* (0.54)	0.79 (0.58)	0.33 (0.59)	1.07* (0.57)	0.01 (0.61)	0.24 (0.6)	—	

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 12. SRP + aPDT |
| 2. Control/no treatment | 13. SRP/flap surgery+ Tinidazole + Ampicillin |
| 3. Intensive OHI | 14. SRP + CHX rinse |
| 4. Supragingival cleaning + AZM | 15. SRP + SZ gel |
| 5. Doxy | 16. SRP + AV gel |
| 6. OHI + SRP | 17. SRP + AZM gel |
| 7. SRP + powered subgingival water irrigation | 18. SRP + CLM gel |
| 8. SRP + SDD | 19. SRP + TET (topical) |
| 9. SRP + Doxy | 20. SRP + TET (topical) + intensive maintenance |
| 10. SRP + AZM | 21. SRP + CHX rinse + Doxy |
| 11. SRP + MTZ + AMX | |

End of study — Periodontal pocket depth (PPD)

The network included 24 trials, 1958 participants and 25 treatments, providing 33 comparisons based on 21 trials with 2 arms, 2 trials with 3 arms and 1 trial with 4 arms. There was no evidence of inconsistency in the network (Figure A8.21).

By the end of the study, compared to control/no treatment, SRP showed no significant effect on reducing PPD; however, the comparison between SRP and supragingival cleaning was statistically significant. There were 4 treatments that showed a significantly better effect than SRP (Table 3.55).

TABLE 3.55 PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.4 (0.31)	—											
3	1.25* (0.52)	0.85 (0.61)	—										
4	0.1 (0.36)	-0.3 (0.47)	-1.15 (0.64)	—									
5	0.35 (0.48)	-0.05 (0.57)	-0.9 (0.7)	0.25 (0.6)	—								
6	-0.07 (0.37)	-0.48 (0.48)	-1.33* (0.65)	-0.18 (0.52)	-0.42 (0.61)	—							
7	-0.33 (0.22)	-0.73* (0.36)	-1.58* (0.57)	-0.43 (0.42)	-0.67 (0.53)	-0.25 (0.43)	—						
8	0.07 (0.27)	-0.33 (0.41)	-1.18* (0.58)	-0.03 (0.45)	-0.28 (0.4)	0.14 (0.46)	0.39 (0.35)	—					
9	-0.2 (0.36)	-0.6 (0.48)	-1.45* (0.64)	-0.3 (0.36)	-0.55 (0.6)	-0.12 (0.52)	0.13 (0.42)	-0.27 (0.45)	—				
10	-0.42 (0.41)	-0.82 (0.51)	-1.67* (0.67)	-0.52 (0.55)	-0.77 (0.63)	-0.35 (0.55)	-0.1 (0.46)	-0.49 (0.49)	-0.22 (0.55)	—			
11	0.1 (0.35)	-0.3 (0.46)	-1.15* (0.62)	0 (0.5)	-0.25 (0.52)	0.17 (0.51)	0.42 (0.4)	0.03 (0.34)	0.3 (0.5)	0.52 (0.54)	—		
12	-0.21 (0.33)	-0.61 (0.38)	-1.47* (0.62)	-0.32 (0.48)	-0.56 (0.58)	-0.14 (0.5)	0.11 (0.35)	-0.28 (0.43)	-0.01 (0.48)	0.21 (0.53)	-0.31 (0.48)	—	
13	-0.47 (0.48)	-0.87* (0.35)	-1.72* (0.71)	-0.57 (0.59)	-0.82 (0.67)	-0.4 (0.59)	-0.15 (0.51)	-0.54 (0.55)	-0.27 (0.6)	-0.05 (0.62)	-0.57 (0.58)	-0.26 (0.52)	—
14	-0.39 (0.37)	-0.79 (0.46)	-1.64* (0.64)	-0.49 (0.52)	-0.74 (0.61)	-0.32 (0.52)	-0.07 (0.38)	-0.46 (0.46)	-0.19 (0.51)	0.03 (0.55)	-0.49 (0.51)	-0.18 (0.42)	0.08 (0.58)
15	-0.52 (0.51)	-0.92 (0.55)	-1.77* (0.72)	-0.62 (0.62)	-0.87 (0.69)	-0.44 (0.63)	-0.19 (0.52)	-0.59 (0.57)	-0.32 (0.62)	-0.1 (0.65)	-0.62 (0.61)	-0.31 (0.38)	-0.05 (0.66)
16	-0.61 (0.49)	-1.01* (0.53)	-1.86* (0.72)	-0.72 (0.59)	-0.96 (0.69)	-0.54 (0.61)	-0.29 (0.51)	-0.68 (0.56)	-0.41 (0.6)	-0.19 (0.64)	-0.71 (0.6)	-0.4 (0.35)	-0.14 (0.64)
17	-0.51 (0.62)	-0.91 (0.65)	-1.76* (0.8)	-0.61 (0.71)	-0.86 (0.77)	-0.44 (0.72)	-0.19 (0.62)	-0.58 (0.67)	-0.31 (0.71)	-0.09 (0.73)	-0.61 (0.7)	-0.3 (0.51)	-0.04 (0.75)
18	-0.94* (0.47)	-1.34* (0.36)	-2.19* (0.7)	-1.04 (0.59)	-1.29* (0.67)	-0.87 (0.6)	-0.62 (0.51)	-1.01 (0.54)	-0.74 (0.6)	-0.52 (0.62)	-1.04 (0.58)	-0.73 (0.53)	-0.47 (0.5)
19	-2.64* (0.34)	-3.04* (0.46)	-3.89* (0.63)	-2.74* (0.5)	-2.99* (0.59)	-2.57* (0.51)	-2.32* (0.41)	-2.71* (0.44)	-2.44* (0.5)	-2.22* (0.54)	-2.74* (0.49)	-2.43* (0.48)	-2.17* (0.58)
20	-0.74*	-1.14*	-1.99*	-0.84	-1.09	-0.67	-0.42	-0.81	-0.54	-0.32	-0.84	-0.53	-0.27

	(0.38)	(0.49)	(0.64)	(0.52)	(0.61)	(0.53)	(0.44)	(0.47)	(0.52)	(0.55)	(0.51)	(0.51)	(0.61)
21	-0.65 (0.43)	-1.05* (0.52)	-1.9* (0.68)	-0.75 (0.56)	-1 (0.65)	-0.58 (0.56)	-0.32 (0.48)	-0.72 (0.51)	-0.45 (0.55)	-0.23 (0.59)	-0.75 (0.55)	-0.44 (0.54)	-0.18 (0.63)
22	0 (0.43)	-0.4 (0.53)	-1.25* (0.69)	-0.1 (0.56)	-0.35 (0.65)	0.07 (0.57)	0.33 (0.49)	-0.07 (0.52)	0.2 (0.56)	0.42 (0.6)	-0.1 (0.55)	0.21 (0.55)	0.47 (0.65)
23	-0.2 (0.49)	-0.6 (0.38)	-1.45* (0.71)	-0.3 (0.6)	-0.55 (0.68)	-0.12 (0.61)	0.13 (0.52)	-0.27 (0.56)	0 (0.6)	0.23 (0.64)	-0.29 (0.6)	0.02 (0.54)	0.28 (0.51)
24	0.15 (0.36)	-0.25 (0.3)	-1.1 (0.63)	0.05 (0.5)	-0.2 (0.59)	0.22 (0.52)	0.48 (0.39)	0.08 (0.44)	0.35 (0.5)	0.57 (0.54)	0.05 (0.49)	0.36 (0.32)	0.62 (0.48)
25	-2.31* (0.56)	-2.71* (0.59)	-3.56* (0.77)	-2.41* (0.66)	-2.66* (0.73)	-2.23* (0.67)	-1.98* (0.58)	-2.38* (0.62)	-2.11* (0.66)	-1.89* (0.7)	-2.41* (0.66)	-2.09* (0.46)	-1.84* (0.7)
T	14	15	16	17	18	19	20	21	22	23	24	25	
14	—												
15	-0.13 (0.57)	—											
16	-0.22 (0.56)	-0.09 (0.52)	—										
17	-0.12 (0.67)	0.01 (0.35)	0.1 (0.62)	—									
18	-0.55 (0.59)	-0.42 (0.66)	-0.33 (0.65)	-0.43 (0.74)	—								
19	-2.25* (0.5)	-2.12* (0.61)	-2.03* (0.6)	-2.13* (0.7)	-1.7* (0.57)	—							
20	-0.35 (0.53)	-0.22 (0.64)	-0.13 (0.63)	-0.23 (0.73)	0.2 (0.61)	1.9* (0.51)	—						
21	-0.26 (0.57)	-0.13 (0.66)	-0.04 (0.65)	-0.14 (0.75)	0.29 (0.63)	1.99* (0.54)	0.09 (0.58)	—					
22	0.39 (0.57)	0.52 (0.67)	0.61 (0.66)	0.51 (0.76)	0.94 (0.64)	2.64* (0.55)	0.74 (0.57)	0.65 (0.6)	—				
23	0.2 (0.6)	0.32 (0.67)	0.42 (0.65)	0.32 (0.76)	0.75 (0.52)	2.45* (0.59)	0.55 (0.63)	0.45 (0.64)	-0.2 (0.65)	—			
24	0.54 (0.47)	0.67 (0.5)	0.76 (0.48)	0.66 (0.61)	1.09* (0.47)	2.79* (0.49)	0.89 (0.53)	0.8 (0.55)	0.15 (0.56)	0.35 (0.48)	—		
25	-1.92* (0.62)	-1.79* (0.6)	-1.69* (0.58)	-1.8* (0.68)	-1.37* (0.69)	0.33 (0.66)	-1.57* (0.68)	-1.66* (0.7)	-2.31* (0.72)	-2.11* (0.7)	-2.46* (0.56)	—	

T: treatment

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 14. SRP + SDD + intensive maintenance |
| 2. Control/no treatment | 15. SRP + Doxy+ intensive maintenance |
| 3. Supragingival cleaning | 16. SRP + MTZ + AMX + intensive maintenance |
| 4. Supragingival cleaning + AZM | 17. SRP+ Doxy+ aPDT + intensive maintenance |
| 5. Doxy | 18. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. SRP + powered subgingival water irrigation | 19. SRP + SZ gel |
| 7. SRP + SDD | 20. SRP + AV gel |
| 8. SRP + Doxy | 21. SRP + AZM gel |
| 9. SRP + AZM | 22. SRP + TET (topical) |
| 10. SRP + ALN | 23. SRP + TET (topical) + intensive maintenance |
| 11. SRP + aPDT | 24. SRP + CHX rinse + intensive maintenance |
| 12. SRP + intensive maintenance | 25. SRP + Doxy gel+ intensive maintenance |
| 13. OHI+ SRP+ intensive maintenance | |

3 months — Clinical attachment level (CAL)

This network meta-analysis included 19 trials, 1835 participants and 19 treatments providing 23 comparisons based on 17 trials with 2 arms and 2 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.24).

The results showed no statistically significant differences between any comparisons in the network (Table 3.56).

TABLE 3.56 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.54 (0.63)	—											
3	0.62 (0.99)	0.08 (0.98)	—										
4	0 (0.77)	-0.54 (0.98)	-0.62 (1.26)	—									
5	0.38 (1.09)	-0.16 (1.27)	-0.23 (1.48)	0.38 (1.35)	—								
6	-0.19 (0.97)	-0.73 (0.73)	-0.81 (1.21)	-0.19 (1.24)	-0.57 (1.47)	—							
7	0.12 (0.77)	-0.42 (1)	-0.5 (1.26)	0.12 (1.09)	-0.26 (1.33)	0.31 (1.25)	—						
8	-0.04 (0.54)	-0.58 (0.83)	-0.66 (1.13)	-0.04 (0.93)	-0.42 (1.23)	0.15 (1.11)	-0.16 (0.94)	—					
9	0.26 (0.54)	-0.28 (0.84)	-0.36 (1.12)	0.26 (0.94)	-0.12 (0.96)	0.45 (1.12)	0.14 (0.93)	0.3 (0.77)	—				
10	-0.2 (0.78)	-0.74 (0.99)	-0.82 (1.26)	-0.2 (0.76)	-0.58 (1.34)	-0.01 (1.24)	-0.32 (1.1)	-0.16 (0.95)	-0.46 (0.94)	—			
11	-0.3 (0.76)	-0.84 (0.99)	-0.92 (1.25)	-0.3 (1.09)	-0.68 (1.33)	-0.11 (1.24)	-0.42 (1.07)	-0.26 (0.93)	-0.56 (0.93)	-0.1 (1.1)	—		
12	0.21 (0.74)	-0.33 (0.97)	-0.4 (1.23)	0.21 (1.05)	-0.17 (1.2)	0.4 (1.21)	0.09 (1.06)	0.25 (0.91)	-0.05 (0.73)	0.41 (1.06)	0.51 (1.06)	—	
13	-0.04 (0.98)	-0.58 (0.76)	-0.66 (1.23)	-0.04 (1.24)	-0.42 (1.48)	0.15 (1.06)	-0.16 (1.26)	0 (1.13)	-0.3 (1.13)	0.16 (1.24)	0.26 (1.24)	-0.25 (1.23)	—
14	0.23 (0.63)	-0.31 (0.61)	-0.38 (0.76)	0.23 (1)	-0.15 (1.26)	0.42 (0.95)	0.11 (1)	0.27 (0.83)	-0.03 (0.83)	0.43 (1)	0.53 (0.99)	0.02 (0.96)	0.27 (0.97)
15	-0.99 (0.74)	-1.53 (0.97)	-1.6 (1.23)	-0.99 (1.07)	-1.37 (1.31)	-0.8 (1.22)	-1.11 (1.06)	-0.95 (0.91)	-1.25 (0.91)	-0.78 (1.06)	-0.69 (1.05)	-1.2 (1.05)	-0.95 (1.22)
16	-0.27 (0.75)	-0.81 (0.98)	-0.88 (1.25)	-0.27 (1.08)	-0.65 (1.33)	-0.08 (1.23)	-0.39 (1.07)	-0.22 (0.93)	-0.53 (0.93)	-0.06 (1.09)	0.04 (1.07)	-0.48 (1.06)	-0.22 (1.24)
17	-0.19 (0.75)	-0.73 (0.99)	-0.81 (1.25)	-0.19 (1.06)	-0.58 (1.32)	0 (1.23)	-0.31 (1.09)	-0.15 (0.93)	-0.45 (0.92)	0.01 (1.07)	0.11 (1.07)	-0.41 (1.05)	-0.15 (1.24)
18	0.41 (0.78)	-0.13 (1.01)	-0.21 (1.26)	0.41 (1.09)	0.03 (1.34)	0.6 (1.26)	0.29 (1.1)	0.45 (0.95)	0.15 (0.95)	0.61 (1.1)	0.71 (1.09)	0.2 (1.08)	0.45 (1.26)
19	0.2 (1)	-0.34 (0.98)	-0.41 (1.09)	0.2 (1.26)	-0.18 (1.48)	0.39 (1.22)	0.08 (1.27)	0.24 (1.13)	-0.06 (1.14)	0.41 (1.27)	0.5 (1.26)	-0.01 (1.24)	0.24 (1.24)
T	14	15	16	17	18	19							
14	—												
15	-1.22 (0.96)	—											
16	-0.5 (0.98)	0.72 (1.06)	—										

17	-0.43 (0.98)	0.79 (1.05)	0.07 (1.07)	—									
18	0.18 (1)	1.4 (1.07)	0.68 (1.08)	0.6 (1.08)	—								
19	-0.03 (0.75)	1.19 (1.23)	0.47 (1.26)	0.4 (1.24)	-0.21 (1.27)	—							

T: treatment

**Legend:

- | | |
|---|---|
| 1. SRP | 11. SRP + MTZ + AMX |
| 2. Control/no treatment | 12. SRP + aPDT |
| 3. Intensive OHI | 13. SRP/flap surgery+ Tinidazole + Ampicillin |
| 4. Supragingival cleaning + AZM | 14. SRP + CHX rinse |
| 5. Doxy | 15. SRP + SZ gel |
| 6. OHI + SRP | 16. SRP + AV gel |
| 7. SRP + powered subgingival water irrigation | 17. SRP + AZM gel |
| 8. SRP + SDD | 18. SRP + TET (topical) |
| 9. SRP + Doxy | 19. SRP + CHX rinse + Doxy |
| 10. SRP + AZM | |

End of study — Clinical attachment level (CAL)

The network included 23 trials, 1950 participants and 24 treatments, providing 32 comparisons based on 20 trials with 2 arms, 2 trials with 3 arms and 1 trial with 4 arms. There was no evidence of inconsistency in the network (Figure A8.26).

By the end of study, compared to control/no treatment, SRP showed no significant effect on reducing CAL. There were 4 treatments that showed a significantly better effect than SRP (Table 3.57).

TABLE 3.57 CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS <65 YR (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.59 (0.33)	—											
3	0.47 (0.41)	-0.12 (0.53)	—										
4	0.1 (0.35)	-0.48 (0.48)	-0.37 (0.54)	—									
5	0.35 (0.73)	-0.24 (0.8)	-0.12 (0.84)	0.24 (0.81)	—								
6	0.12 (0.38)	-0.47 (0.5)	-0.35 (0.55)	0.01 (0.51)	-0.23 (0.82)	—							
7	-0.53* (0.21)	-1.12* (0.37)	-1* (0.46)	-0.63 (0.41)	-0.88 (0.75)	-0.65 (0.43)	—						
8	0.16 (0.26)	-0.42 (0.42)	-0.31 (0.49)	0.06 (0.44)	-0.18 (0.68)	0.05 (0.46)	0.69* (0.33)	—					
9	0.1 (0.34)	-0.49 (0.48)	-0.37 (0.53)	0 (0.34)	-0.24 (0.81)	-0.01 (0.51)	0.63 (0.4)	-0.06 (0.43)	—				
10	-0.52 (0.37)	-1.1* (0.49)	-0.99 (0.55)	-0.62 (0.51)	-0.86 (0.82)	-0.63 (0.53)	0.01 (0.42)	-0.68 (0.46)	-0.62 (0.5)	—			
11	0.17 (0.39)	-0.42 (0.5)	-0.31 (0.57)	0.06 (0.52)	-0.18 (0.78)	0.05 (0.54)	0.69 (0.44)	0 (0.37)	0.06 (0.52)	0.68 (0.53)	—		
12	-0.14	-0.73*	-0.61	-0.24	-0.49	-0.26	0.39	-0.3	-0.24	0.38	-0.3	—	

	(0.31)	(0.36)	(0.52)	(0.47)	(0.79)	(0.49)	(0.32)	(0.41)	(0.47)	(0.48)	(0.49)		
13	-0.19 (0.45)	-0.78* (0.31)	-0.66 (0.62)	-0.3 (0.57)	-0.54 (0.86)	-0.31 (0.58)	0.34 (0.48)	-0.36 (0.52)	-0.29 (0.57)	0.33 (0.58)	-0.36 (0.59)	-0.05 (0.47)	—
14	-0.89* (0.32)	-1.48* (0.42)	-1.36* (0.52)	-1* (0.48)	-1.24 (0.79)	-1.01* (0.49)	-0.36 (0.32)	-1.06* (0.41)	-1* (0.47)	-0.38 (0.49)	-1.06* (0.5)	-0.75* (0.35)	-0.7 (0.52)
15	-0.53 (0.55)	-1.12* (0.58)	-1 (0.69)	-0.63 (0.65)	-0.88 (0.91)	-0.65 (0.67)	0 (0.56)	-0.69 (0.61)	-0.63 (0.65)	-0.01 (0.66)	-0.69 (0.67)	-0.39 (0.46)	-0.34 (0.66)
16	-0.54 (0.46)	-1.13* (0.5)	-1.01 (0.62)	-0.65 (0.59)	-0.89 (0.86)	-0.66 (0.6)	-0.01 (0.48)	-0.71 (0.54)	-0.64 (0.58)	-0.03 (0.59)	-0.71 (0.6)	-0.4 (0.35)	-0.35 (0.59)
17	-0.61 (0.65)	-1.2 (0.68)	-1.08 (0.78)	-0.72 (0.75)	-0.96 (0.97)	-0.73 (0.75)	-0.08 (0.66)	-0.78 (0.7)	-0.71 (0.74)	-0.1 (0.74)	-0.78 (0.76)	-0.47 (0.58)	-0.42 (0.75)
18	0.01 (0.45)	-0.58 (0.3)	-0.46 (0.62)	-0.1 (0.57)	-0.34 (0.85)	-0.11 (0.58)	0.54 (0.48)	-0.16 (0.52)	-0.09 (0.57)	0.53 (0.58)	-0.16 (0.59)	0.15 (0.47)	0.2 (0.43)
19	-2.28* (0.31)	-2.87* (0.45)	-2.75* (0.51)	-2.38* (0.47)	-2.63* (0.79)	-2.4* (0.48)	-1.75* (0.37)	-2.44* (0.41)	-2.38* (0.47)	-1.76* (0.48)	-2.44* (0.49)	-2.14* (0.43)	-2.09* (0.55)
20	-0.6 (0.32)	-1.19* (0.47)	-1.07* (0.52)	-0.71 (0.48)	-0.95 (0.79)	-0.72 (0.5)	-0.07 (0.38)	-0.77 (0.41)	-0.7 (0.47)	-0.09 (0.49)	-0.77 (0.5)	-0.46 (0.45)	-0.41 (0.56)
21	-0.6 (0.33)	-1.19* (0.46)	-1.07* (0.54)	-0.7 (0.49)	-0.95 (0.8)	-0.72 (0.5)	-0.07 (0.39)	-0.76 (0.42)	-0.7 (0.48)	-0.08 (0.5)	-0.77 (0.5)	-0.46 (0.45)	-0.41 (0.55)
22	-0.19 (0.37)	-0.77 (0.49)	-0.66 (0.55)	-0.29 (0.5)	-0.53 (0.82)	-0.3 (0.52)	0.34 (0.42)	-0.35 (0.45)	-0.29 (0.5)	0.33 (0.52)	-0.35 (0.54)	-0.05 (0.48)	0.01 (0.58)
23	0.34 (0.36)	-0.25 (0.28)	-0.13 (0.55)	0.24 (0.51)	0 (0.81)	0.23 (0.52)	0.87* (0.39)	0.18 (0.45)	0.24 (0.5)	0.86 (0.51)	0.18 (0.52)	0.48 (0.31)	0.53 (0.42)
24	-2.46* (0.6)	-3.04* (0.63)	-2.93* (0.74)	-2.56* (0.7)	-2.8* (0.94)	-2.57* (0.72)	-1.93* (0.61)	-2.62* (0.65)	-2.56* (0.7)	-1.94* (0.7)	-2.62* (0.71)	-2.32* (0.52)	-2.26* (0.7)
T	14	15	16	17	18	19	20	21	22	23	24		
14	—												
15	0.36 (0.58)	—											
16	0.35 (0.5)	-0.01 (0.57)	—										
17	0.28 (0.68)	-0.08 (0.36)	-0.07 (0.67)	—									
18	0.9 (0.53)	0.54 (0.66)	0.55 (0.59)	0.62 (0.74)	—								
19	-1.39* (0.44)	-1.75* (0.63)	-1.74* (0.56)	-1.67* (0.72)	-2.29* (0.55)	—							
20	0.29 (0.46)	-0.07 (0.64)	-0.06 (0.57)	0.01 (0.73)	-0.61 (0.56)	1.68* (0.44)	—						
21	0.29 (0.46)	-0.07 (0.64)	-0.06 (0.57)	0.01 (0.73)	-0.61 (0.55)	1.68* (0.44)	0 (0.46)	—					
22	0.71 (0.48)	0.34 (0.66)	0.36 (0.59)	0.43 (0.74)	-0.19 (0.58)	2.09* (0.48)	0.42 (0.49)	0.41 (0.5)	—				
23	1.24* (0.43)	0.87 (0.56)	0.88 (0.47)	0.95 (0.66)	0.33 (0.42)	2.62* (0.47)	0.94* (0.49)	0.94* (0.48)	0.53 (0.51)	—			
24	-1.56* (0.63)	-1.93* (0.7)	-1.91* (0.63)	-1.84* (0.79)	-2.46* (0.71)	-0.18 (0.68)	-1.85* (0.69)	-1.86* (0.69)	-2.27* (0.71)	-2.8* (0.61)	—		

T: treatment

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 13. OHI+ SRP+ intensive maintenance |
| 2. Control/no treatment | 14. SRP + SDD + intensive maintenance |
| 3. Supragingival cleaning | 15. SRP + Doxy+ intensive maintenance |
| 4. Supragingival cleaning + AZM | 16. SRP + MTZ + AMX + intensive maintenance |
| 5. Doxy | 17. SRP+ Doxy+ aPDT + intensive maintenance |
| 6. SRP + powered subgingival water irrigation | 18. SRP/flap surgery+ Tinidazole + Ampicillin |
| 7. SRP + SDD | 19. SRP + SZ gel |
| 8. SRP + Doxy | 20. SRP + AV gel |
| 9. SRP + AZM | 21. SRP + AZM gel |
| 10. SRP + ALN | 22. SRP + TET (topical) |
| 11. SRP + aPDT | 23. SRP + CHX rinse + intensive maintenance |
| 12. SRP + intensive maintenance | 24. SRP + Doxy gel+ intensive maintenance |

TYPE OF DIABETES MELLITUS

TYPE 2 DM

3 months — Hemoglobin A1C (HbA1c)

The network informing the effect of periodontal treatments in type 2 diabetic patients at 3 months included 28 trials, 2079 participants and 21 treatments providing 38 comparisons based on 23 trials with 2 arms and 5 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.7).

Compared with control/no treatment, SRP could significantly reduce the HbA1c level (mean difference was -0.34%; 95% CI: -0.66% to -0.02%). One treatment (“SRP plus systemic doxycycline, topical aPDT and intensive maintenance”) showed a significantly better effect than SRP (mean difference was -2.01%; 95% CI: -3.85% to -0.18%). (Table 3.58)

TABLE 3.58 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH DM 2 (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.34* (0.16)	—											
3	0.25 (0.54)	-0.09 (0.51)	—										
4	0.22 (0.35)	-0.12 (0.31)	-0.03 (0.55)	—									
5	-0.37 (0.46)	-0.71 (0.46)	-0.62 (0.69)	-0.59 (0.55)	—								
6	-0.03 (0.49)	-0.37 (0.51)	-0.28 (0.72)	-0.25 (0.60)	0.34 (0.67)	—							
7	-0.44 (0.39)	0.78* (0.35)	-0.69 (0.62)	-0.66 (0.47)	-0.07 (0.57)	-0.41 (0.62)	—						
8	-0.37 (0.34)	-0.71 (0.37)	-0.62 (0.63)	-0.59 (0.48)	0.00 (0.57)	-0.34 (0.59)	0.07 (0.51)	—					
9	-0.23 (0.18)	0.56* (0.22)	-0.47 (0.56)	-0.45 (0.38)	0.15 (0.49)	-0.20 (0.46)	0.22 (0.41)	0.15 (0.36)	—				
10	0.12 (0.45)	-0.22 (0.48)	-0.13 (0.70)	-0.10 (0.57)	0.49 (0.64)	0.15 (0.67)	0.56 (0.59)	0.49 (0.56)	0.35 (0.48)	—			
11	0.28 (0.34)	-0.06 (0.38)	0.03 (0.64)	0.06 (0.49)	0.65 (0.57)	0.31 (0.60)	0.72 (0.52)	0.65 (0.48)	0.51 (0.38)	0.16 (0.56)	—		
12	-0.14 (0.28)	-0.48 (0.33)	-0.38 (0.61)	-0.36 (0.45)	0.24 (0.54)	-0.11 (0.56)	0.30 (0.48)	0.23 (0.44)	0.09 (0.32)	-0.26 (0.53)	-0.42 (0.45)	—	
13	-0.93 (0.57)	- 1.27*	-1.18 (0.77)	-1.15 (0.65)	-0.56 (0.34)	-0.90 (0.75)	-0.49 (0.66)	-0.56 (0.66)	-0.70 (0.59)	-1.05 (0.72)	-1.21 (0.66)	-0.79 (0.64)	—

		(0.57)											
14	-1.54 (0.81)	1.88* (0.81)	-1.79 (0.96)	1.76* (0.87)	-1.17 (0.68)	-1.51 (0.95)	-1.10 (0.88)	-1.17 (0.88)	-1.32 (0.83)	-1.66 (0.92)	1.82* (0.88)	-1.40 (0.87)	-0.61 (0.59)
15	-0.03 (0.84)	-0.36 (0.84)	-0.27 (0.98)	-0.25 (0.89)	0.35 (0.71)	0.00 (0.97)	0.42 (0.91)	0.35 (0.90)	0.20 (0.85)	-0.15 (0.95)	-0.31 (0.91)	0.11 (0.89)	0.90 (0.62)
16	2.01* (0.93)	2.34* (0.93)	2.25* (1.06)	2.23* (0.98)	1.63* (0.82)	-1.98 (1.05)	-1.56 (0.99)	-1.63 (0.99)	-1.78 (0.94)	2.13* (1.03)	2.29* (0.99)	-1.87 (0.97)	-1.08 (0.75)
17	-0.02 (0.37)	-0.36 (0.33)	-0.27 (0.61)	-0.24 (0.45)	0.35 (0.56)	0.01 (0.61)	0.42 (0.48)	0.35 (0.50)	0.21 (0.40)	-0.14 (0.58)	-0.30 (0.50)	0.12 (0.47)	0.91 (0.66)
18	0.04 (0.28)	-0.30 (0.23)	-0.21 (0.46)	-0.18 (0.31)	0.41 (0.51)	0.07 (0.56)	0.48 (0.42)	0.41 (0.44)	0.27 (0.32)	-0.08 (0.53)	-0.24 (0.44)	0.18 (0.40)	0.97 (0.61)
19	0.01 (0.33)	-0.33 (0.37)	-0.24 (0.63)	-0.21 (0.48)	0.38 (0.56)	0.04 (0.59)	0.45 (0.51)	0.38 (0.47)	0.23 (0.37)	-0.11 (0.56)	-0.27 (0.47)	0.15 (0.44)	0.94 (0.65)
20	-0.01 (0.34)	-0.35 (0.38)	-0.26 (0.64)	-0.23 (0.49)	0.36 (0.57)	0.02 (0.60)	0.43 (0.52)	0.36 (0.48)	0.22 (0.39)	-0.13 (0.56)	-0.29 (0.48)	0.13 (0.45)	0.92 (0.66)
21	0.24 (0.41)	-0.10 (0.38)	-0.01 (0.64)	0.02 (0.49)	0.61 (0.59)	0.27 (0.64)	0.68 (0.52)	0.61 (0.53)	0.47 (0.44)	0.12 (0.61)	-0.04 (0.53)	0.38 (0.50)	1.17 (0.68)
T	14	15	16	17	18	19	20	21					
14	—												
15	1.52 (0.86)	—											
16	-0.46 (0.46)	1.98* (0.98)	—										
17	1.52 (0.88)	0.01 (0.90)	1.99* (0.98)	—									
18	1.58 (0.84)	0.07 (0.87)	2.05* (0.95)	0.06 (0.40)	—								
19	1.55 (0.88)	0.04 (0.90)	2.01* (0.98)	0.03 (0.49)	-0.03 (0.43)	—							
20	1.53 (0.88)	0.02 (0.90)	1.99* (0.99)	0.01 (0.50)	-0.05 (0.44)	-0.02 (0.48)	—						
21	1.78* (0.89)	0.27 (0.92)	2.25* (1.00)	0.26 (0.51)	0.20 (0.45)	0.23 (0.53)	0.25 (0.54)	—					

T: treatment

* Statistically significant

**Legend:

- | | |
|-----------------------------|---|
| 1. SRP | 12. SRP + aPDT |
| 2. Control/no treatment | 13. SRP + intensive maintenance |
| 3. Intensive OHI | 14. SRP + Doxy + intensive maintenance |
| 4. CHX rinse | 15. SRP + AMX + intensive maintenance |
| 5. Supragingival cleaning | 16. SRP+ Doxy+ aPDT + intensive maintenance |
| 6. Doxy | 17. SRP/flap surgery+ Tinidazole + Ampicillin |
| 7. OHI + SRP | 18. SRP + CHX rinse |
| 8. SRP + SDD | 19. SRP + SMV gel |
| 9. SRP + Doxy | 20. SRP + TET (topical) |
| 10. SRP + MTZ + AMX | 21. SRP + TET (topical) + intensive maintenance |
| 11. SRP + Omega 3 + aspirin | |

End of study — Hemoglobin A1C (HbA1c)

This network informing effect of periodontal treatments on type 2 diabetic patients by end of study included 30 trials, 2143 participants and 24 providing 42 comparisons based on 24 trials with 2 arms and 6 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.15).

By the end of study, SRP showed a significant effect on reducing HbA1c (mean difference was -0.40%; 95% CI: -0.75% to -0.09%). There were no statistical differences between other treatments and SRP (Table 3.59).

TABLE 3.59 HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH DM 2 (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.40* (0.16)	—											
3	0.01 (0.56)	-0.39 (0.54)	—										
4	0.14 (0.34)	-0.26 (0.30)	0.13 (0.53)	—									
5	0.34 (0.30)	-0.05 (0.29)	0.34 (0.61)	0.20 (0.42)	—								
6	-0.02 (0.47)	-0.42 (0.49)	-0.03 (0.73)	-0.16 (0.58)	-0.36 (0.55)	—							
7	-0.36 (0.32)	0.76* (0.37)	-0.37 (0.65)	-0.50 (0.47)	-0.71 (0.44)	-0.34 (0.56)	—						
8	-0.22 (0.16)	0.62* (0.21)	-0.23 (0.57)	-0.36 (0.37)	-0.56 (0.33)	-0.20 (0.44)	0.14 (0.35)	—					
9	-0.20 (0.78)	-0.59 (0.79)	-0.20 (0.96)	-0.34 (0.85)	-0.54 (0.83)	-0.18 (0.91)	0.17 (0.84)	0.02 (0.79)	—				
10	-0.02 (0.31)	-0.42 (0.35)	-0.03 (0.64)	-0.16 (0.46)	-0.37 (0.43)	0.00 (0.57)	0.34 (0.45)	0.20 (0.35)	0.17 (0.84)	—			
11	-0.14 (0.26)	-0.54 (0.30)	-0.15 (0.62)	-0.28 (0.43)	-0.48 (0.39)	-0.12 (0.53)	0.22 (0.42)	0.08 (0.30)	0.06 (0.82)	-0.12 (0.41)	—		
12	-0.12 (0.31)	-0.52 (0.28)	-0.13 (0.60)	-0.26 (0.41)	-0.46 (0.29)	-0.10 (0.56)	0.24 (0.45)	0.10 (0.34)	0.08 (0.83)	-0.10 (0.44)	0.02 (0.40)	—	
13	-0.24 (0.37)	-0.64 (0.34)	-0.25 (0.64)	-0.39 (0.46)	-0.59 (0.40)	-0.22 (0.59)	0.12 (0.50)	-0.03 (0.40)	-0.05 (0.86)	-0.22 (0.49)	-0.10 (0.45)	-0.12 (0.34)	—
14	-0.66 (0.37)	1.06* (0.34)	-0.67 (0.63)	-0.81 (0.45)	1.01* (0.45)	-0.64 (0.60)	-0.30 (0.50)	-0.45 (0.40)	-0.47 (0.86)	-0.64 (0.49)	-0.52 (0.45)	-0.54 (0.44)	-0.42 (0.48)
15	-0.71 (0.66)	-1.11 (0.64)	-0.72 (0.83)	-0.85 (0.71)	-1.05 (0.65)	-0.69 (0.80)	-0.35 (0.74)	-0.49 (0.67)	-0.51 (1.02)	-0.69 (0.73)	-0.57 (0.71)	-0.59 (0.58)	-0.46 (0.67)
16	0.77 (0.69)	0.37 (0.68)	0.76 (0.86)	0.62 (0.74)	0.42 (0.68)	0.79 (0.83)	1.13 (0.76)	0.98 (0.70)	0.96 (1.03)	0.79 (0.76)	0.91 (0.73)	0.89 (0.61)	1.01 (0.70)
17	0.70 (0.61)	0.30 (0.59)	0.69 (0.79)	0.56 (0.66)	0.36 (0.59)	0.72 (0.77)	1.06 (0.69)	0.92 (0.62)	0.90 (0.99)	0.72 (0.68)	0.84 (0.66)	0.82 (0.52)	0.94 (0.62)
18	-1.16 (0.79)	1.56* (0.77)	-1.17 (0.94)	-1.31 (0.83)	-1.51 (0.78)	-1.14 (0.91)	-0.80 (0.86)	-0.95 (0.80)	-0.97 (1.10)	-1.14 (0.84)	-1.02 (0.83)	-1.04 (0.72)	-0.92 (0.79)
19	0.04 (0.34)	-0.36 (0.30)	0.03 (0.61)	-0.11 (0.43)	-0.31 (0.42)	0.06 (0.58)	0.40 (0.47)	0.25 (0.37)	0.23 (0.85)	0.06 (0.46)	0.18 (0.43)	0.16 (0.41)	0.28 (0.46)
20	-0.19 (0.35)	-0.59 (0.31)	-0.20 (0.44)	-0.33 (0.30)	-0.53 (0.43)	-0.17 (0.58)	0.17 (0.48)	0.03 (0.37)	0.01 (0.85)	-0.17 (0.47)	-0.05 (0.43)	-0.07 (0.42)	0.05 (0.46)
21	0.02 (0.30)	-0.38 (0.34)	0.01 (0.64)	-0.12 (0.46)	-0.32 (0.43)	0.04 (0.56)	0.38 (0.44)	0.24 (0.34)	0.22 (0.83)	0.04 (0.43)	0.16 (0.40)	0.14 (0.43)	0.26 (0.48)
22	-0.01 (0.31)	-0.41 (0.36)	-0.02 (0.64)	-0.15 (0.47)	-0.36 (0.44)	0.01 (0.57)	0.35 (0.45)	0.21 (0.35)	0.18 (0.84)	0.01 (0.44)	0.13 (0.41)	0.11 (0.44)	0.23 (0.49)
23	0.19 (0.38)	-0.20 (0.34)	0.18 (0.64)	0.05 (0.46)	-0.15 (0.45)	0.21 (0.60)	0.56 (0.50)	0.41 (0.40)	0.39 (0.86)	0.21 (0.50)	0.33 (0.46)	0.31 (0.44)	0.44 (0.49)
24	0.49 (0.35)	0.09 (0.31)	0.48 (0.62)	0.35 (0.43)	0.14 (0.42)	0.51 (0.58)	0.85 (0.48)	0.71 (0.37)	0.68 (0.85)	0.51 (0.47)	0.63 (0.43)	0.61 (0.40)	0.73 (0.46)

T	14	15	16	17	18	19	20	21	22	23	24		
14	—												
15	-0.04 (0.73)	—											
16	1.43 (0.76)	1.47 (0.83)	—										
17	1.37* (0.68)	1.41 (0.78)	-0.06 (0.80)	—									
18	-0.50 (0.84)	-0.46 (0.43)	1.93* (0.94)	1.86* (0.89)	—								
19	0.70 (0.45)	0.74 (0.71)	-0.73 (0.74)	-0.66 (0.66)	1.20 (0.83)	—							
20	0.48 (0.45)	0.52 (0.71)	-0.95 (0.74)	-0.89 (0.66)	0.98 (0.83)	-0.23 (0.43)	—						
21	0.68 (0.48)	0.73 (0.73)	-0.75 (0.75)	-0.68 (0.68)	1.18 (0.84)	-0.02 (0.46)	0.21 (0.46)	—					
22	0.65 (0.49)	0.70 (0.73)	-0.78 (0.76)	-0.71 (0.68)	1.15 (0.85)	-0.05 (0.46)	0.18 (0.47)	-0.03 (0.44)	—				
23	0.86 (0.48)	0.90 (0.73)	-0.57 (0.76)	-0.51 (0.69)	1.36 (0.84)	0.16 (0.46)	0.38 (0.46)	0.17 (0.49)	0.20 (0.50)	—			
24	1.15* (0.46)	1.20 (0.70)	-0.28 (0.73)	-0.21 (0.66)	1.65* (0.82)	0.45 (0.43)	0.68 (0.44)	0.47 (0.46)	0.50 (0.47)	0.30 (0.46)	—		

T: treatment

* Statistically significant

**Legend:

- | | | |
|---------------------------|--|---|
| 1. SRP | 9. SRP + ALN | 17. SRP + MTZ + AMX + intensive maintenance |
| 2. Control/no treatment | 10. SRP + Omega 3 + aspirin | 18. SRP+ Doxy+ aPDT + intensive maintenance |
| 3. Intensive OHI | 11. SRP + aPDT | 19. SRP/flap surgery+ Tinidazole + Ampicillin |
| 4. CHX rinse | 12. SRP + intensive maintenance | 20. SRP + CHX rinse |
| 5. Supragingival cleaning | 13. SRP + non-intensive maintenance | 21. SRP + SMV gel |
| 6. Doxy | 14. OHI+ SRP+ intensive maintenance | 22. SRP + TET (topical) |
| 7. SRP + SDD | 15. SRP + Doxy + intensive maintenance | 23. SRP + TET (topical) + intensive maintenance |
| 8. SRP + Doxy | 16. SRP + AMX + intensive maintenance | 24. SRP + CHX rinse + intensive maintenance |

TYPE 1 DM

There was no analysis for type 1 DM patients only.

TYPE 2 DM AND TYPE 1 DM

End of study — Hemoglobin A1C (HbA1c)

The network informing effect of periodontal treatments in patients with either type 1 or type 2 diabetes mellitus included 3 trials, 488 participants and 7 treatments providing 10 comparisons based on 1 trial with 2 arms, 1 trial with 3 arms and the third with 4 arms (Figure 3.17). The network lacks a closed loop and consistency tests could not be performed.

Control/no treatment was not involved in this network meta-analysis and the results showed no statistically significant differences between any comparisons (Table 3.60).

FIGURE 3.17 EVIDENCE NETWORK FOR HBA1C WITH MIXED DM AT END OF STUDY

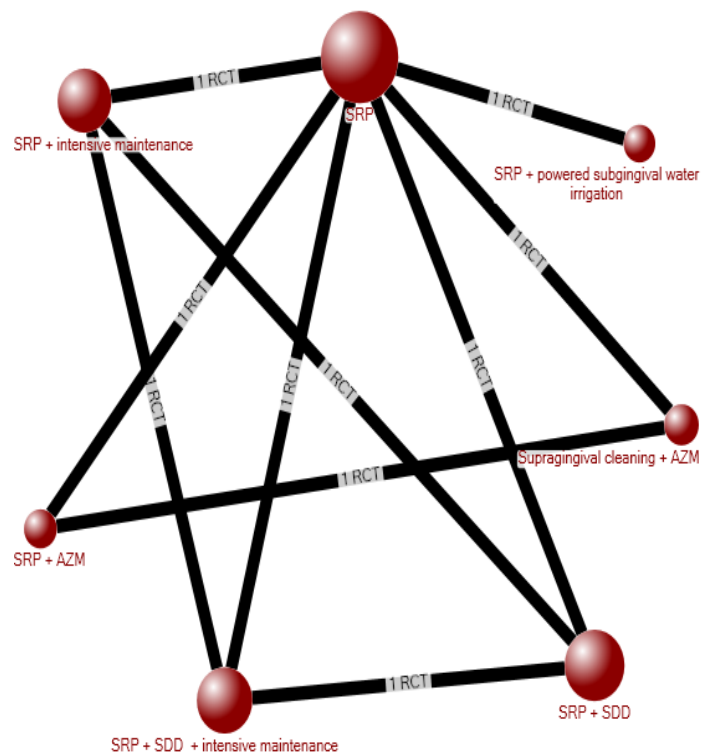


TABLE 3.60 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH MIXED DM (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7
1	—						
2	0.11 (2.91)	—					
3	-0.18 (2.90)	-0.28 (4.13)	—				
4	0.27 (2.93)	0.16 (4.14)	0.44 (4.13)	—			
5	-0.59 (2.91)	-0.70 (2.93)	-0.42 (4.14)	-0.86 (4.13)	—		
6	-0.32 (2.94)	-0.43 (4.16)	-0.15 (4.13)	-0.59 (2.92)	0.27 (4.13)	—	
7	0.34 (2.92)	0.23 (4.14)	0.51 (4.11)	0.07 (2.91)	0.93 (4.14)	0.66 (2.92)	—

**Legend:

- | | |
|---|--------------------------------------|
| 1. SRP | 5. SRP + AZM |
| 2. Supragingival cleaning + AZM | 6. SRP + intensive maintenance |
| 3. SRP + powered subgingival water irrigation | 7. SRP + SDD + intensive maintenance |
| 4. SRP + SDD | |

BASELINE PPD LEVEL

PPD <5MM

3 months — Hemoglobin A1C (HbA1c)

The network informing the effect of periodontal treatments in patients with baseline PPD less than 5mm included 23 trials, 2199 participant and 17 treatments, providing 33 comparisons based on 18 trials with 2 arms and 5 trials with 3 arms. There was no evidence of inconsistency in the network (Figure A8.8).

Compared with control/no treatment, SRP had a significant effect on reducing HbA1c (mean difference was -0.33%; 95% CI: -0.65% to -0.03%). There were no statistically significant differences between other treatments and SRP (Table 3.61).

TABLE 3.61 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE PPD< 5MM (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.33* (0.15)	—								
3	0.52 (0.54)	0.20 (0.52)	—							
4	-0.37 (0.44)	-0.70 (0.44)	-0.90 (0.67)	—						
5	0.81 (0.46)	0.48 (0.49)	0.29 (0.70)	1.18 (0.64)	—					
6	-0.03 (0.46)	-0.36 (0.48)	-0.55 (0.70)	0.34 (0.63)	-0.84 (0.66)	—				
7	-0.45 (0.34)	-0.78* (0.31)	-0.97 (0.60)	-0.08 (0.54)	-1.26* (0.58)	-0.42 (0.57)	—			
8	-0.16 (0.42)	-0.49 (0.44)	-0.68 (0.68)	0.21 (0.60)	-0.97 (0.63)	-0.13 (0.62)	0.29 (0.54)	—		
9	-0.11 (0.24)	-0.43 (0.29)	-0.63 (0.59)	0.27 (0.50)	-0.92 (0.52)	-0.08 (0.52)	0.34 (0.42)	0.06 (0.49)	—	
10	-0.22 (0.16)	-0.55* (0.20)	-0.75 (0.55)	0.15 (0.46)	-1.04* (0.49)	-0.19 (0.44)	0.23 (0.37)	-0.06 (0.45)	-0.12 (0.28)	—
11	-0.19 (0.46)	-0.51 (0.48)	-0.71 (0.70)	0.19 (0.63)	-1.00* (0.46)	-0.16 (0.65)	0.26 (0.57)	-0.02 (0.63)	-0.08 (0.51)	0.04 (0.48)
12	0.13 (0.42)	-0.20 (0.45)	-0.40 (0.68)	0.50 (0.61)	-0.69 (0.63)	0.16 (0.62)	0.58 (0.54)	0.29 (0.60)	0.23 (0.48)	0.35 (0.45)
13	-0.15 (0.25)	-0.47 (0.29)	-0.67 (0.59)	0.23 (0.50)	-0.96 (0.53)	-0.11 (0.52)	0.31 (0.42)	0.02 (0.49)	-0.04 (0.35)	0.08 (0.28)
14	-0.03 (0.32)	-0.36 (0.29)	-0.55 (0.59)	0.34 (0.52)	-0.84 (0.57)	0.00 (0.56)	0.42 (0.42)	0.13 (0.53)	0.07 (0.40)	0.19 (0.35)
15	0.32 (0.32)	-0.01 (0.29)	-0.20 (0.43)	0.69 (0.52)	-0.49 (0.56)	0.35 (0.56)	0.77 (0.42)	0.48 (0.53)	0.42 (0.40)	0.54 (0.35)

16	0.23 (0.38)	-0.10 (0.34)	-0.30 (0.62)	0.60 (0.55)	-0.59 (0.60)	0.26 (0.59)	0.68 (0.46)	0.39 (0.56)	0.33 (0.45)	0.45 (0.40)
17	0.45 (0.45)	0.12 (0.43)	-0.07 (0.53)	0.82 (0.61)	-0.36 (0.64)	0.48 (0.64)	0.90 (0.53)	0.61 (0.61)	0.56 (0.51)	0.67 (0.47)
Treatment	11	12	13	14	15	16	17			
11	—									
12	0.31 (0.62)	—								
13	0.04 (0.52)	-0.27 (0.49)	—							
14	0.15 (0.56)	-0.16 (0.53)	0.11 (0.41)	—						
15	0.51 (0.56)	0.19 (0.53)	0.46 (0.41)	0.35 (0.41)	—					
16	0.41 (0.59)	0.10 (0.56)	0.37 (0.45)	0.26 (0.45)	-0.09 (0.45)	—				
17	0.64 (0.64)	0.32 (0.61)	0.60 (0.51)	0.48 (0.51)	0.13 (0.31)	0.22 (0.55)	—			

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 10. SRP + Doxy |
| 2. Control/no treatment | 11. SRP + AZM |
| 3. Intensive OHI | 12. SRP + MTZ + AMX |
| 4. Supragingival cleaning | 13. SRP + aPDT |
| 5. Supragingival cleaning + AZM | 14. SRP/flap surgery+ Tinidazole + Ampicillin |
| 6. Doxy | 15. SRP + CHX rinse |
| 7. OHI + SRP | 16. SRP + TET (topical) + intensive maintenance |
| 8. SRP + powered subgingival water irrigation | 17. SRP + CHX rinse + Doxy |
| 9. SRP + SDD | |

End of study — Hemoglobin A1C (HbA1c)

The network informing effect of periodontal treatments in patients with baseline PPD less than 5mm included 25 trials, 2224 participants and 22 treatments providing 42 comparisons based on 18 trials with 2 arms, 6 trials with 3 arms and 1 trial with 4 arms. There was no evidence of inconsistency in the network (Figure A8.16).

SRP showed a significant effect on reducing HbA1c level (mean difference was -0.36%; 95% CI: -0.71% to -0.04%). No statistically significant differences were found between other periodontal therapies and SRP (Table 3.62).

TABLE 3.62 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF SUTDY IN PATIENTS WITH BASELINE PPD< 5MM (RANDOM-EFFECTS NMA; MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.36* (0.17)	—											
3	-0.24 (0.42)	-0.60 (0.42)	—										
4	0.12 (0.46)	-0.24 (0.49)	0.36 (0.63)	—									
5	-0.02	-0.38	0.22	-0.14	—								

	(0.46)	(0.48)	(0.62)	(0.65)									
6	-0.17 (0.42)	-0.53 (0.45)	0.07 (0.59)	-0.29 (0.62)	-0.15 (0.62)	—							
7	-0.13 (0.26)	-0.49 (0.30)	0.11 (0.49)	-0.25 (0.54)	-0.11 (0.52)	0.04 (0.49)	—						
8	-0.21 (0.16)	-0.57* (0.21)	0.03 (0.44)	-0.33 (0.49)	-0.19 (0.43)	-0.04 (0.44)	-0.08 (0.29)	—					
9	-0.59 (0.48)	-0.94 (0.51)	-0.34 (0.64)	-0.70 (0.45)	-0.56 (0.66)	-0.42 (0.63)	-0.45 (0.55)	-0.37 (0.50)	—				
10	-0.22 (0.80)	-0.58 (0.82)	0.02 (0.90)	-0.34 (0.93)	-0.20 (0.93)	-0.05 (0.90)	-0.09 (0.84)	-0.01 (0.82)	0.36 (0.94)	—			
11	-0.15 (0.25)	-0.50 (0.30)	0.10 (0.49)	-0.26 (0.53)	-0.12 (0.52)	0.02 (0.49)	-0.01 (0.36)	0.07 (0.28)	0.44 (0.54)	0.08 (0.84)	—		
12	-0.19 (0.30)	-0.55* (0.28)	0.05 (0.49)	-0.31 (0.55)	-0.17 (0.54)	-0.02 (0.51)	-0.05 (0.36)	0.02 (0.33)	0.40 (0.56)	0.03 (0.85)	-0.04 (0.39)	—	
13	-0.29 (0.36)	-0.65* (0.34)	-0.05 (0.53)	-0.41 (0.59)	-0.27 (0.58)	-0.12 (0.55)	-0.16 (0.43)	-0.08 (0.39)	0.29 (0.60)	-0.07 (0.88)	-0.15 (0.44)	-0.11 (0.33)	—
14	-0.70 (0.36)	-1.06* (0.32)	-0.46 (0.52)	-0.81 (0.58)	-0.68 (0.58)	-0.53 (0.55)	-0.56 (0.44)	-0.48 (0.38)	-0.11 (0.59)	-0.48 (0.88)	-0.55 (0.44)	-0.51 (0.43)	-0.40 (0.46)
15	0.23 (0.40)	-0.13 (0.42)	0.48 (0.57)	0.12 (0.61)	0.25 (0.61)	0.40 (0.58)	0.37 (0.41)	0.45 (0.43)	0.82 (0.62)	0.45 (0.90)	0.38 (0.48)	0.42 (0.43)	0.53 (0.50)
16	-0.77 (0.64)	-1.13 (0.63)	-0.53 (0.75)	-0.89 (0.79)	-0.75 (0.78)	-0.60 (0.75)	-0.64 (0.67)	-0.56 (0.65)	-0.19 (0.80)	-0.55 (1.03)	-0.63 (0.69)	-0.58 (0.57)	-0.48 (0.66)
17	0.71 (0.68)	0.35 (0.67)	0.95 (0.79)	0.59 (0.81)	0.73 (0.82)	0.88 (0.79)	0.84 (0.70)	0.92 (0.69)	1.29 (0.82)	0.93 (1.05)	0.85 (0.73)	0.90 (0.61)	1.00 (0.70)
18	0.64 (0.59)	0.28 (0.58)	0.88 (0.70)	0.52 (0.74)	0.66 (0.74)	0.81 (0.72)	0.77 (0.62)	0.85 (0.60)	1.23 (0.75)	0.86 (0.98)	0.79 (0.64)	0.83 (0.51)	0.93 (0.61)
19	-1.23 (0.77)	-1.59* (0.76)	-0.99 (0.86)	-1.35 (0.90)	-1.21 (0.89)	-1.06 (0.86)	-1.10 (0.79)	-1.02 (0.78)	-0.64 (0.90)	-1.01 (1.12)	-1.08 (0.81)	-1.04 (0.71)	-0.94 (0.78)
20	0.00 (0.33)	-0.36 (0.28)	0.24 (0.51)	-0.12 (0.57)	0.02 (0.56)	0.17 (0.53)	0.13 (0.41)	0.21 (0.35)	0.58 (0.58)	0.22 (0.87)	0.14 (0.41)	0.18 (0.40)	0.29 (0.44)
21	0.16 (0.37)	-0.20 (0.33)	0.40 (0.53)	0.04 (0.59)	0.18 (0.59)	0.33 (0.56)	0.29 (0.45)	0.37 (0.39)	0.74 (0.61)	0.38 (0.88)	0.30 (0.45)	0.35 (0.43)	0.45 (0.47)
22	0.44 (0.33)	0.09 (0.29)	0.69 (0.51)	0.33 (0.57)	0.47 (0.56)	0.61 (0.53)	0.58 (0.41)	0.66 (0.35)	1.03 (0.58)	0.67 (0.86)	0.59 (0.41)	0.63 (0.39)	0.74 (0.44)
T	14	15	16	17	18	19	20	21	22				
14	—												
15	0.93 (0.53)	—											
16	-0.08 (0.71)	-1.01 (0.71)	—										
17	1.40 (0.75)	0.47 (0.74)	1.48 (0.83)	—									
18	1.34 (0.66)	0.41 (0.67)	1.41 (0.76)	-0.07 (0.80)	—								
19	-0.53 (0.83)	-1.46 (0.83)	-0.46 (0.42)	-1.94* (0.93)	-1.87* (0.87)	—							
20	0.69 (0.42)	-0.24 (0.51)	0.77 (0.69)	-0.71 (0.73)	-0.64 (0.64)	1.23 (0.81)	—						
21	0.86 (0.46)	-0.07 (0.54)	0.93 (0.71)	-0.55 (0.75)	-0.48 (0.67)	1.39 (0.83)	0.16 (0.44)	—					
22	1.14* (0.43)	0.21 (0.51)	1.22 (0.69)	-0.26 (0.73)	-0.20 (0.64)	1.67* (0.81)	0.45 (0.41)	0.28 (0.44)	—				

T: treatment

* Statistically significant

**Legend:

- | | | |
|---|---------------------------------------|---|
| 1. SRP | 9. SRP + AZM | 17. SRP + AMX+ intensive maintenance |
| 2. Control/no treatment | 10. SRP + ALN | 18. SRP + MTZ + AMX + intensive maintenance |
| 3. Supragingival cleaning | 11. SRP + aPDT | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 4. Supragingival cleaning + AZM | 12. SRP + intensive maintenance | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 5. Doxy | 13. SRP + non-intensive maintenance | 21. SRP + TET (topical) + intensive maintenance |
| 6. SRP + powered subgingival water irrigation | 14. OHI+ SRP+ intensive maintenance | 22. SRP + CHX rinse + intensive maintenance |
| 7. SRP + SDD | 15. SRP + SDD + intensive maintenance | |
| 8. SRP + Doxy | 16. SRP + Doxy+ intensive maintenance | |

PPD BETWEEN 5-7MM

3 months — Hemoglobin A1C (HbA1c)

This network informing effect of periodontal treatments in patients with PPD between 5-7mm included 3 trials, 90 participants and 3 treatments providing 3 comparisons based on 3 trials each with 2 arms (Figure 3.18). The network lacks a closed loop and consistency tests could not be performed.

There were no statistically significant differences between any comparisons within the network meta-analysis (Table 3.63).

FIGURE 3.18 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS IN PATIENTS WITH BASELINE PPD BETWEEN 5-7MM

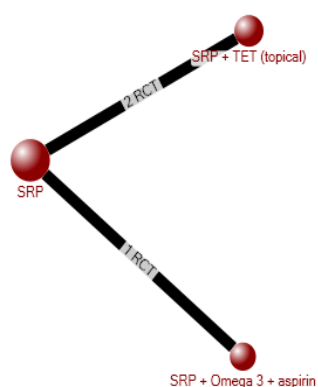


TABLE 3.63 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE PPD BETWEEN 5-7MM (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3
1	—		
2	0.28 (1.87)	—	
3	-0.02 (1.33)	-0.30 (2.30)	—

**Legend:

1. SRP

2. SRP + Omega 3 + aspirin

3. SRP + TET (topical)

PPD >7MM

There was no analysis for this subgroup.

BASELINE HbA1c LEVEL

HbA1c < 7%

3 months — Hemoglobin A1C (HbA1c)

This network informing effect of periodontal treatments in patients with baseline HbA1c <7% included 3 trials, 99 participants and 4 treatments providing 3 comparisons based on 3 trials each with 2 arms (Figure 3.19). The network lacks closed a loop and consistency tests could not be performed.

There were no statistically significant differences between any comparisons within the network meta-analysis (Table 3.64).

FIGURE 3.19 EVIDENCE NETWORK FOR HbA1c AT 3 MONTHS IN PATIENTS WITH BASELINE HbA1c <7%

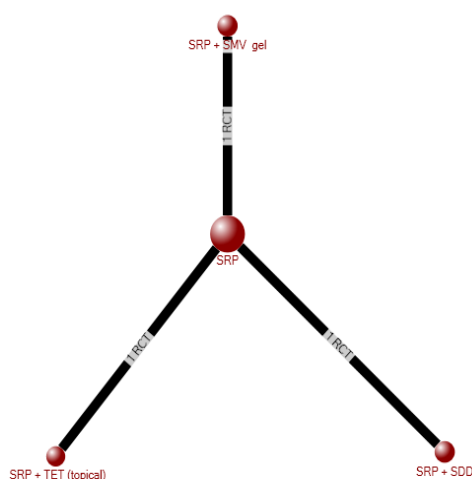


TABLE 3.64 HbA1c -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE HbA1c <7% (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4
1	—			
2	-0.08 (2.90)	—		
3	0.00 (2.90)	0.09 (4.08)	—	
4	-0.03 (2.92)	0.05 (4.13)	-0.04 (4.12)	—

**Legend:

1. SRP

2. SRP + SDD

3. SRP + SMV gel

4. SRP + TET (topical)

End of study — Hemoglobin A1C (HbA1c)

As in the network meta-analysis at 3 months, this network by end of study included 3 trials, 99 participants and 4 treatments, providing 3 comparisons based on 3 trials each with 2 arms (Figure 3.20). The network lacks a closed loop and consistency tests could not be performed.

There were no statistically significant differences between any comparisons in the network meta-analysis (Table 3.65).

FIGURE 3.20 EVIDENCE NETWORK FOR HBA1C AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C <7%

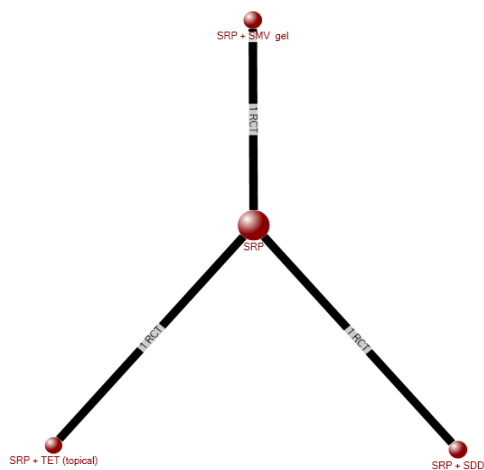


TABLE 3.65 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C <7% (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4
1	—			
2	-0.08 (2.90)	—		
3	0.01 (2.90)	0.10 (4.08)	—	
4	-0.03 (2.92)	0.05 (4.13)	-0.05 (4.12)	—

**Legend:

1. SRP

2. SRP + SDD

3. SRP + SMV gel

4. SRP + TET (topical)

HbA1c BETWEEN 7- 8%

There was no analysis for this subgroup.

HbA1c > 8%

3 months — Hemoglobin A1C (HbA1c)

This network informing effect of periodontal treatments in patients with baseline HbA1c >8% included 4 trials with 446 participants and 6 treatments, providing 6 comparisons based on 3 trials with 2 arms and 1 trial with 3 arms (Figure 3.21). The network lacks a closed loop and consistency tests could not be performed.

There were no statistically significant differences between any comparisons (Table 3.66).

FIGURE 3.21 EVIDENCE NETWORK FOR HBA1C AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C >8%

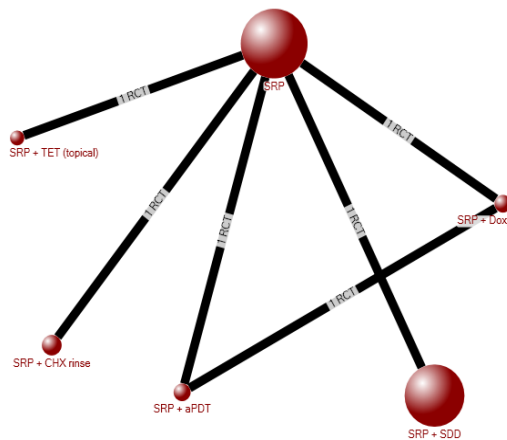


TABLE 3.66 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS IN PATIENTS WITH BASELINE HBA1C >8% (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6
1	—					
2	0.18 (2.91)	—				
3	-0.19 (2.94)	-0.37 (4.12)	—			
4	0.06 (2.93)	-0.12 (4.11)	0.25 (2.97)	—		
5	-0.08 (3.09)	-0.26 (4.24)	0.11 (4.24)	-0.14 (4.27)	—	
6	-0.05 (2.93)	-0.23 (4.15)	0.14 (4.16)	-0.11 (4.15)	0.03 (4.25)	—

**Legend:

- | | | |
|---------------|--------------------|------------------------|
| 1. SRP | 4. SRP + SDD | 3. SRP + Doxy |
| 2. SRP + aPDT | 5. SRP + CHX rinse | 6. SRP + TET (topical) |

End of study — Hemoglobin A1C (HbA1c)

This network meta-analysis by end of study included 5 trials, 496 participants and 9 treatments, providing 12 comparisons based on 3 trials with 2 arms, 1 trial with 3 arms and 1 trial with 4 arms (Figure 3.22). Consistency could not be assessed.

There were no statistically significant differences between any comparisons (Table 3.67).

FIGURE 3.22 EVIDENCE NETWORK FOR HBA1C AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C >8%

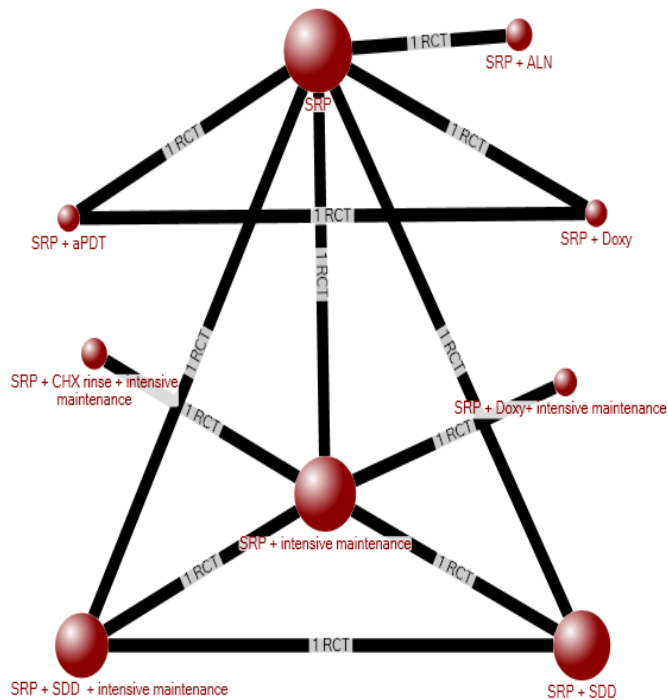


TABLE 3.67 HBA1C -- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY IN PATIENTS WITH BASELINE HBA1C >8% (RANDOM-EFFECTS NMA; MEAN±SD)

Treatment**	1	2	3	4	5	6	7	8	9
1	—								
2	0.26 (2.91)	—							
3	-0.18 (2.92)	-0.44 (4.12)	—						
4	-0.23 (2.99)	-0.49 (4.17)	-0.05 (4.17)	—					
5	0.08 (2.95)	-0.18 (4.15)	0.26 (2.95)	0.31 (4.19)	—				
6	-0.29 (2.89)	-0.55 (2.94)	-0.11 (4.09)	-0.06 (4.14)	-0.37 (4.14)	—			
7	0.36 (2.91)	0.10 (2.92)	0.54 (4.12)	0.59 (4.18)	0.28 (4.15)	0.65 (2.94)	—		
8	-0.89 (4.10)	-1.15 (4.15)	-0.71 (5.03)	-0.66 (5.06)	-0.97 (5.06)	-0.60 (2.93)	-1.25 (4.15)	—	
9	0.79 (4.24)	0.53 (4.27)	0.97 (5.14)	1.02 (5.17)	0.71 (5.17)	1.08 (3.09)	0.43 (4.26)	1.68 (4.27)	—

**Legend:

- | | | |
|---------------|--------------------------------|--|
| 1. SRP | 4. SRP + ALN | 7. SRP + SDD + intensive maintenance |
| 2. SRP + SDD | 5. SRP + aPDT | 8. SRP + Doxy+ intensive maintenance |
| 3. SRP + Doxy | 6. SRP + intensive maintenance | 9. SRP + CHX rinse + intensive maintenance |

3.4 SAFETY OUTCOMES

Before data extraction, we listed adverse effects that we might encounter. These consisted of serious adverse and common adverse effects related to periodontal treatments. Serious adverse events were defined as events that resulted in hospitalization or death. The common adverse effects included acute inflammation of periodontal tissue, pain, bleeding, loosening of the teeth, headache, dizziness, gastrointestinal disturbances, nausea/vomiting, diarrhea, metallic taste, irritability, thermal sensitivity and dry mouth. In addition to adverse events mentioned above, all withdrawals (includes any reason) and withdrawals due to adverse effects were also classed as safety outcomes.

After data extraction, it appeared that safety outcomes were poorly reported across all included studies. Safety outcome data were collected through self-reported questionnaires or telephone calls. Except total withdrawals (includes any reason), statistical analyses for other safety outcomes were not feasible. Instead of doing meta-analyses, here we conducted a descriptive analysis.

Total withdrawals (includes any reason)

Twenty-eight trials reported number of withdrawals. The network comprised 24 treatments, and included 40 comparisons based on 22 trials with 2 arms and 6 trials with 3 arms. Deviance information criterions of the fixed- and random-effects model were very similar. Because the random-effects model incorporated heterogeneity, results from the random-effects model were reported in the text. Results from the fixed-effects model were listed in Appendix 9. No statistically significant differences were found between any periodontal treatments and control/no treatment (Table 3.68). There was no evidence of inconsistency in the network (Figure A8.33).

TABLE 3.68 TOTAL WITHDRAWALS (RANDOM-EFFECTS NMA; RELATIVE RISK $\pm$ 95% CREDIBLE INTERVAL)

T**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	1.75 (0.83,3.5)	—										
3	0.58 (0,13.2)	0.33 (0,7.62)	—									
4	1 (0.21,3.72)	0.57 (0.13,2.05)	1.85 (0.05,186.5)	—								
5	0.63 (0.12,2.79)	0.35 (0.06,1.94)	1.13 (0.02,187)	0.63 (0.08,5.21)	—							
6	2.96 (0.79,10.32)	1.72 (0.37,6.8)	5.04 (0.14,731.7)	2.95 (0.48,21.75)	4.76 (0.64,36.55)	—						
7	0.98 (0.36,2.55)	0.56 (0.16,1.94)	1.73 (0.06,228.1)	0.98 (0.18,5.61)	1.57 (0.24,10.49)	0.33 (0.08,1.27)	—					
8	0.84 (0.2,3.27)	0.48 (0.1,2.35)	1.42 (0.04,254.9)	0.86 (0.11,6.87)	1.37 (0.3,6.13)	0.29 (0.04,1.95)	0.86 (0.14,5.28)	—				
9	1.68 (0.45,5.45)	0.95 (0.3,2.65)	3.07 (0.08,343.7)	1.65 (0.5,6.58)	2.71 (0.35,18.88)	0.57 (0.09,3.42)	1.7 (0.33,8.45)	1.95 (0.31,12.32)	—			
10	0.97	0.56	1.81	0.99	1.58	0.33	1.01	1.15	0.58	—		

	(0.15,5.4 9)	(0.1,2.74)	(0.04,329)	(0.12,7.2)	(0.14,15. 62)	(0.03,2.9 9)	(0.11,7.5 9)	(0.12,11)	(0.09,3.1 3)			
11	2.04 (0.37,7.5 7)	1.16 (0.24,4.0 5)	3.46 (0.09,553 .2)	2.02 (0.25,14. 27)	3.24 (0.34,26. 1)	0.68 (0.08,4.5 9)	2.14 (0.25,10. 86)	2.33 (0.29,17. 47)	1.21 (0.18,6.4 9)	2.02 (0.23,17. 8)	—	
12	0.46 (0.04,3.5 3)	0.27 (0.02,1.7 4)	0.86 (0.01,121 .3)	0.46 (0.04,4.0 6)	0.76 (0.04,9.7 6)	0.16 (0.01,1.8 4)	0.46 (0.03,4.7 7)	0.54 (0.03,6.4 5)	0.28 (0.03,1.3 7)	0.48 (0.03,5.3 2)	0.23 (0.01,2.5 5)	—
13	0.78 (0.03,10. 98)	0.46 (0.02,7.4 7)	1.5 (0.02,261 .1)	0.78 (0.03,17. 32)	1.23 (0.04,29. 11)	0.27 (0.01,4.9 3)	0.82 (0.04,12. 31)	0.93 (0.03,19. 16)	0.47 (0.02,8.9 7)	0.77 (0.03,24. 78)	0.39 (0.01,9.1 8)	1.76 (0.05,54. 52)
14	1.13 (0.14,6.1 7)	0.66 (0.07,3.8)	2.04 (0.05,234 .1)	1.09 (0.09,12. 13)	1.77 (0.12,20. 35)	0.36 (0.03,3.1 1)	1.16 (0.12,6.9 1)	1.31 (0.09,12. 61)	0.69 (0.05,5.5 2)	1.15 (0.06,14. 48)	0.57 (0.04,6.2 8)	2.44 (0.13,54. 58)
15	0.97 (0.01,15. 25)	0.54 (0.9.13)	1.52 (0.377.7)	0.96 (0.01,24. 62)	1.44 (0.01,41. 94)	0.32 (0.7.47)	0.98 (0.01,18. 33)	1.06 (0.01,28. 26)	0.55 (0.12.75)	0.93 (0.01,28. 32)	0.44 (0.11.04)	1.87 (0.01,127 .5)
16	1.07 (0.01,14. 27)	0.63 (0.01,8.3 7)	1.7 (0.42,9.2 6)	0.94 (0.01,25. 95)	1.66 (0.01,48. 19)	0.35 (0.7.77)	1.09 (0.01,17. 28)	1.32 (0.01,28. 43)	0.62 (0.01,13. 89)	1.05 (0.01,30. 65)	0.54 (0.12.34)	1.97 (0.02,118 .2)
17	1.3 (0.25,6.0 7)	0.75 (0.12,4.0 1)	2.48 (0.06,331 .7)	1.31 (0.16,10. 85)	2.06 (0.22,19. 25)	0.44 (0.05,3.4 7)	1.35 (0.19,8.2 7)	1.57 (0.18,12. 91)	0.77 (0.1,5.96)	1.41 (0.12,13. 71)	0.65 (0.07,7.2 1)	2.89 (0.22,54. 24)
18	0.58 (0.01,12. 47)	0.33 (0.7.4)	0.96 (0.523.3)	0.59 (0.01,18. 65)	0.95 (0.01,30. 65)	0.2 (0.5.07)	0.58 (0.01,15. 38)	0.71 (0.01,21. 76)	0.34 (0.10.28)	0.58 (0.01,24. 59)	0.31 (0.7.74)	1.24 (0.01,77. 37)
19	1.36 (0.25,6.1 9)	0.78 (0.12,4.2 9)	2.39 (0.07,327 .2)	1.31 (0.15,13. 71)	2.15 (0.22,19. 95)	0.46 (0.05,3.0 3)	1.42 (0.19,8.1 4)	1.57 (0.18,14. 06)	0.8 (0.11,6.6 1)	1.36 (0.11,17. 04)	0.67 (0.07,6.2 7)	2.87 (0.24,52. 12)
20	0.99 (0.03,10. 34)	0.56 (0.02,6.9 2)	1.68 (0.02,394 .6)	0.97 (0.03,14. 83)	1.55 (0.04,27. 03)	0.32 (0.01,5.0 5)	1 (0.03,13. 34)	1.15 (0.04,18. 28)	0.6 (0.02,8.1 5)	1.02 (0.03,18. 15)	0.48 (0.01,9.0 5)	2.09 (0.05,60. 23)
21	1.72 (0.19,12. 87)	0.98 (0.11,8.3 2)	3.09 (0.06,712 .4)	1.76 (0.15,19. 1)	2.76 (0.2,39.7 9)	0.58 (0.05,7.2 3)	1.82 (0.17,15. 93)	2.02 (0.17,26. 02)	1.08 (0.09,11. 21)	1.75 (0.11,31. 81)	0.89 (0.07,11. 86)	4.01 (0.21,80. 9)
22	0.7 (0.12,3.4)	0.4 (0.06,2.2 5)	1.18 (0.04,181 .9)	0.74 (0.07,5.4 4)	1.14 (0.12,9.6 3)	0.24 (0.03,1.8 2)	0.72 (0.1,4.52)	0.82 (0.09,6.7)	0.43 (0.05,3.1 8)	0.73 (0.06,8.1 4)	0.35 (0.04,3.6 9)	1.61 (0.11,27. 08)
23	0.85 (0.14.3)	0.49 (0.8.03)	1.45 (0.344.8)	0.84 (0.18.64)	1.22 (0.40.23)	0.28 (0.8.67)	0.85 (0.19.58)	0.99 (0.28.67)	0.53 (0.9.84)	0.9 (0.14.72)	0.4 (0.13.17)	1.8 (0.01,72. 69)
24	1.34	0.76	2.3	1.32	2.14	0.44	1.37	1.59	0.79	1.37	0.67	2.82

	(0.44,3.57)	(0.34,1.6)	(0.09,282)	(0.32,6.47)	(0.33,14.62)	(0.08,2.38)	(0.3,5.55)	(0.26,8.64)	(0.25,2.66)	(0.23,8.69)	(0.14,3.52)	(0.4,38.45)
T	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	1.4 (0.05,43.7)	—										
15	1.06 (0,106.3)	0.9 (0,24.14)	—									
16	1.21 (0.01,90.37)	0.91 (0.01,27.03)	1.16 (0.01,298.1)	—								
17	1.62 (0.08,63.37)	1.19 (0.11,16.82)	1.39 (0.05,248.6)	1.34 (0.05,165.3)	—							
18	0.69 (0,65.59)	0.58 (0,24.17)	0.75 (0,172.2)	0.53 (0,252.7)	0.44 (0,16.69)	—						
19	1.59 (0.07,55.54)	1.25 (0.09,15.94)	1.42 (0.05,236.5)	1.29 (0.06,133.5)	1.04 (0.1,8.95)	2.24 (0.06,169.9)	—					
20	1.29 (0.01,47.61)	0.9 (0.02,18.1)	0.99 (0.02,262.9)	0.87 (0.01,174.1)	0.71 (0.02,13.64)	1.78 (0.02,180)	0.76 (0.02,12.25)	—				
21	2.3 (0.08,75.2)	1.59 (0.1,28.4)	2.04 (0.04,455.1)	1.8 (0.05,291.7)	1.33 (0.09,20)	2.97 (0.06,311.4)	1.32 (0.09,18.41)	1.75 (0.07,87.71)	—			
22	0.93 (0.04,26.27)	0.65 (0.05,9.04)	0.75 (0.03,151.4)	0.65 (0.03,73.21)	0.55 (0.05,4.9)	1.22 (0.03,122.1)	0.55 (0.05,5.06)	0.74 (0.03,30.96)	0.41 (0.03,5.84)	—		
23	1.03 (0,68.6)	0.67 (0,31.23)	0.88 (0,307.7)	0.86 (0,161.4)	0.65 (0,16.99)	1.36 (0,210.1)	0.62 (0,21.18)	1 (0,60.97)	0.44 (0,17.48)	1.15 (0,32.98)	—	
24	1.6 (0.09,43.33)	1.16 (0.15,13.32)	1.4 (0.07,228.5)	1.21 (0.08,144.8)	1.01 (0.15,7.25)	2.27 (0.09,168.1)	1 (0.14,6.86)	1.36 (0.1,38.43)	0.76 (0.08,7.7)	1.89 (0.29,15.07)	1.58 (0.09,437.5)	—

T: treatment

**Legend:

- | | | |
|---------------------------------|--|---|
| 1. SRP | 9. SRP + intensive maintenance | 17. SRP + SZ gel |
| 2. Control/no treatment | 10. SRP + non-intensive maintenance | 18. SRP + AV gel |
| 3. Intensive OHI | 11. OHI+ SRP+ intensive maintenance | 19. SRP + AZM gel |
| 4. Supragingival cleaning | 12. SRP + MTZ + AMX + intensive maintenance | 20. SRP + ALN gel |
| 5. Supragingival cleaning + AZM | 13. SRP + powered subgingival water irrigation | 21. SRP + SMV gel |
| 6. SRP + SDD | 14. SRP + aPDT | 22. SRP + CLM gel |
| 7. SRP + Doxy | 15. CHX rinse | 23. SRP + TET (topical) + non-intensive maintenance |
| 8. SRP + AZM | 16. SRP + CHX rinse | 24. SRP + CHX rinse + intensive maintenance |

Serious adverse events

Four studies (Macedo 2013; Santos 2009; Skaleric 2004; Pradeep 2015) reported that all subjects completed the trials and no adverse effects/major adverse effects were reported by any of the subjects. This could be interpreted as no serious adverse effects in these studies. Engebretson 2013 reported safety population and stated that no study related serious adverse events occurred. There were 16 other studies reporting no adverse effects/major adverse effects but that had dropouts. None of them provided the safety population. We may surmise zero serious adverse effects but the data were not convincing.

Common adverse effects

The situation is similar as regards to common adverse effects related to periodontal treatment. Six studies reported specific adverse effects and only Engebretson 2013 provided both the safety population and number of events in each arm. The safety population of another study (Miranda 2014) can be inferred from the flow chart. Another 4 studies only report the number of adverse events but did not give the number of patients who actually received the treatments.

Engebretson 2013 was a two-arm RCT. The treatment group received the combined treatment of SRP plus CHX rinse and maintenance; while the control group received no treatment. The safety population in the test and control group was 254 and 257 respectively. More patients suffered from pain in the test group (102/254) than controls (72/257) and more patients reported thermal sensitivity in the test group (81/254) than controls (47/257). Differences were significant for both adverse effects between groups.

Miranda 2014 was also a two-arm study. In the treatment arm, 29 patients received SRP combined with systemic MTZ, AMX and maintenance. Out of the 29 patients, 7 reported diarrheas, 4 had headache, 4 had metallic taste and 5 suffered nausea/vomiting. In the control arm, 27 patients received SRP plus placebo treatment. Three, 1, 2 and 2 patients reported diarrheas, headache, metallic taste and nausea/vomiting respectively. No one had irritability in either group. No statistically significant differences were found between groups.

Chen 2012 stated that “no patients reported acute onset of periodontal infection”. Al-Zahrani 2009 indicated that “none of the patients reported any complications associated with the use of PDT therapy, such as burning sensations, discomfort or pain”. Tsalikis 2014 found dizziness and difficulty to swallow in one female participant in the control group. Botero2013 had only one patient who reported gastrointestinal disturbances in the placebo group. None of these authors reported the number of patients who received treatments.

Except for the studies mentioned above, the others either gave a vague summary with no safety population or did not mention adverse effects at all. No articles reported bleeding, loosening of the teeth and dry mouth.

Withdrawals due to adverse effects

Ten trials were completed with no patients lost to follow up (Macedo 2013; Moeintaghavi 2012; Santos 2012; Deo 2010; Santos 2009; Skaleric 2004; Telgi 2013; Artese 2015; Pradeep 2015; Koçak 2016). This means that there were no withdrawals due to adverse effects. One trial (Chen 2012) reported in their flow chart that 2 patients withdrew due to a broken arm or leg. Since we decided to take a broad view, withdrawals due to adverse effects, which may not be caused directly by periodontal therapy, were also taken into consideration. The rest of the trials had no available information as regards to withdrawals due to adverse effects.

CHAPTER 4: DISCUSSION

4.1 SUMMARY

We have performed a comprehensive systematic review and network meta-analysis evaluating the effects of periodontal therapy on glycemic control and clinical periodontal status. Except for fructosamine, CRP and GCF volume, 6 out of 9 outcomes had sufficient data for network meta-analysis.

Compared with control/no treatment, the standard treatment of SRP significantly reduced serum HbA1c at 3 months and by the end of study. One treatment of “SRP plus systematic used Doxy, locally used aPDT and intensive maintenance” showed a significantly better effect than SRP in reducing HbA1c at 3 months. We found no statistical differences between other periodontal treatments and SRP by the end of study.

SRP has long been known as a first-line treatment for periodontitis. Several periodontal therapies appeared to be more effective than SRP on improving periodontal status (i.e. PPD; CAL; BOP; PI; GI); however, the effect varied by antibiotics, route of administration and treatment combination.

Nine treatments (out of 26 treatments) had a significantly better PPD outcome than SRP at 3 months and the number increased to 12 (out of 36 treatments) by the end of study. For the outcome of CAL, 3 (out of 24 treatments) and 10 treatments (out of 31 treatments) showed a significantly better effect than SRP at 3 months and by the end of study respectively. SRP plus EO-based rinse was more effective than SRP for improving BOP and PI at both assessment times. By the end of study, “SRP plus systemic SMV” also showed better effects than SRP on improving BOP and 5 more treatments showed a better effect than SRP on improving PI. As for the outcome of GI, “SRP plus systemic Omega 3 and aspirin” and “SRP plus SZ gel” were found to be more effective than SRP at 3 months. The significant effect attenuated to non-significant by the end of study.

There were limited data with which to investigate the benefits of periodontal therapy on HbA1c level by participant age (< v. > 65 yr.), type of diabetes mellitus (type 1 v. 2 v. 1&2), baseline PPD level (<5 v. 5-7 v. >7mm) as well as baseline HbA1c level (<7% v. 7-8% v. >8%). Based on limited data, we found that there were no differences in HbA1c

level among patients who received periodontal treatments and control/no treatment given the age less than 65 years. There were no data for patients who were at least 65 years old. Among the patients who were diagnosed with type 2 DM, results of the network meta-analysis were consistent with the base case. For trials that recruited both type 1 and type 2 diabetic patients, a network meta-analysis showed no differences between any periodontal treatments by the end of study. Analyzable subgroup network meta-analyses that were based on baseline characteristics suggested SRP had a significant effect on reducing HbA1c level. No differences were found between any other comparisons.

Safety outcomes were poorly reported in most studies. Network meta-analysis could only be performed for total withdrawals (include any reason). The results showed no statistically significant differences between any comparisons in the network. For other safety outcomes, 2 patients withdrew due to a broken arm or leg and no patient reported severe adverse event directly caused by periodontal treatments. Common adverse events were reported in some trials; however no meta-analysis could be performed.

4.2 CONTEXT

To our best knowledge, this is the first network meta-analysis evaluating periodontal therapies on blood glycemic control and clinical periodontal situations in patients diagnosed with both diabetes mellitus and periodontitis.

4.2.1 PRIMARY OUTCOME (HEMOGLOBIN A1C)

SRP has been widely considered as the standard treatment of periodontitis. In our network meta-analysis, it showed a significant effect on reducing serum HbA1c in patients with both periodontitis and diabetes mellitus at both 3 months and the end of study, relative to control/no treatment. The results were based on random-effects network meta-analysis models, which were congruent with both fixed-effects network meta-analysis models and direct evidence.

Although no network meta-analysis had been previously performed, there were 12 previous systematic reviews and meta-analyses that compared the effect of all periodontal

treatments against control/no treatment. Ten of these reviews suggested periodontal therapies had the effect of improving HbA1c levels in diabetic patients. Most of the periodontal treatments in previous reviews were combined treatments incorporating SRP with antibiotics and/or photodynamic therapy and/or maintenance. SRP could be considered as the basis of these combined periodontal treatments. Results of previous systematic reviews and meta-analyses were not contradictory with ours and our findings added to their credibility regarding the effects of SRP on glycemic control.

We found one combined treatment (SRP + systematic used Doxy + locally used aPDT + intensive maintenance) that showed a better effect than SRP at 3 months in terms of HbA1c. This suggests combination therapy may have a better effect than the monotherapy of SRP; however, this result should be interpreted with caution since this combination therapy was connected to the network by only one trial (Macedo 2013) with a small sample size of 30 (2 arm trial with 15 pts in each arm). Moreover, patients recruited in this trial had poor glycemic control at baseline (mean of HbA1c: 8.33%), which may reduce the generalizability of the results.

Previous studies yielded inconsistent results regarding the effect of adjunctive antibiotics on glycemic control. By the end of study, the significant effect of the combination therapy at 3 months attenuated and was non-significant. No differences were found between other periodontal therapies and SRP. That is to say, by the end of study, adjunctive use of antibiotics had no effect on reducing HbA1c. This finding is contradicted by results of many included RCTs, but consistent with the two previous meta-analyses that had subgroup analyses stratified by antibiotic use (Liew 2013; Corbella 2013). In the review of Liew 2013, studies using adjunctive antibiotics, whether systemic or topical, had a non-significant overall effect as compared to control/no treatment. In Corbella 2013, they compared periodontal non-surgical treatment alone vs treatment with adjunctive antimicrobial devices. No significant differences were found, favouring non-surgical treatment alone.

4.2.2 SECONDARY OUTCOMES

SRP had a significant effect on improving all of the periodontal parameters that were included in the network meta-analyses. Several combination therapies were associated with a better effect compared to SRP monotherapy. These were consistent with the findings in previous systematic reviews/meta-analyses evaluating the effectiveness of antimicrobial agents as an adjunct to SRP in the general population (i.e. not specific to patients with DM) [74-76]

Periodontal probing depth (PPD)

At 3 months, we found SRP had a significantly better effect than control/no treatment and intensive OHI on improving PPD level. This is in line with the current knowledge of periodontal treatment. Nine combined treatments showed a significantly better effect than SRP. They are OHI+ SRP; SRP + MTZ + AMX; SRP + Omega 3 + aspirin; SRP/flap surgery+ Tinidazole + Ampicillin; SRP + SZ gel; SRP + AV gel; SRP + ALN gel; SRP + SMV gel and SRP + CLM gel.

By the end of study, SRP still had a significantly better effect than control/no treatment; however, there was no difference between SRP and intensive OHI. Twelve combined treatments were significantly better than SRP: SRP + SDD; SRP + Omega 3 + aspirin; OHI+ SRP+ intensive maintenance; SRP/flap surgery+ Tinidazole + Ampicillin; SRP + SMV gel; SRP + CLM gel; SRP + SZ gel; SRP + AV gel; SRP + AZM gel; SRP + ALN gel; SRP + TET (topical) + non-intensive maintenance and SRP + Doxy gel+ intensive maintenance.

Trials and treatments included in these two network meta-analyses were not exactly the same; this may partially explain the differences in their findings. By comparison, we found that SRP + Omega 3 + aspirin; SRP/flap surgery+ Tinidazole + Ampicillin; SRP + SZ gel; SRP + AV gel; SRP + ALN gel; SRP + SMV gel and SRP + CLM gel were significantly better than SRP monotherapy at both 3 months and end of study. This suggests adjunctive antibiotics /surgical treatment could increase the effect of SRP; however, when it comes to a specific antibiotic/surgical treatment, the results should be interpreted with caution. Except for the adjunctive use of SDD, all other combination therapies were connected to the network by one study each. Out of these studies, only Pradeep 2013 was judged as having a low risk of bias.

Clinical attachment level (CAL)

Compared to control/no treatment, SRP had a significant effect on improving CAL at both 3 months and the end of study. At 3 months, SRP + SZ gel; SRP + ALN gel and SRP + SMV gel showed a significantly better effect than SRP monotherapy. By the end of study, 10 combined treatments (SRP + SDD; SRP + SDD + intensive maintenance; SRP + SMV gel; SRP + CLM gel; SRP + SZ gel; SRP + AV gel; SRP + AZM gel; SRP + ALN gel; SRP + TET (topical) + non-intensive maintenance; SRP + Doxy gel+ intensive maintenance) showed a significantly better effect than SRP monotherapy.

Two combination treatments (SRP + ALN gel; SRP + SZ gel) were significantly better than SRP monotherapy at both 3 months and end of study. Similar to the outcome of PPD, this finding suggests adjunctive use of antibiotics, either systemic or topically applied, may increase the effect of SRP. However, due to a small number of trials for each head to head comparison in the network meta-analysis, findings should be interpreted with caution.

Bleeding on probing (BOP)

Bleeding on probing reflects the inflammation of gingival tissue. Compared to control/no treatment, SRP showed a significant effect on alleviate gingiva inflammation at 3 months and the end of study. SRP plus EO-based rinse had a significantly better effect than SRP at 3 months and the end of study. By the end of study, SRP + SMV gel also showed significantly better effect than SRP.

EO-based rinse may have an adjunctive effect on reducing gingival inflammation; however, this result is based on one trial (Alshehri 2015) judged as unclear for overall risk of bias. Similarly, as to the effect of adjunctive antibiotics, it is uncertain due to limited data. Clear cut conclusions could not be made and more studies are warranted.

Plaque index (PI)

PI is the index of oral hygiene situation. As compared to control/no treatment, SRP had a significant effect on improving oral hygiene at 3 months and the end of study. At 3 months, SRP + EO-based rinse had significant better effect than SRP. By the end of study, 6 therapies (Intensive OHI; CHX rinse; OHI+ SRP+ intensive maintenance; SRP + CHX rinse; SRP + EO-based rinse; SRP + CHX rinse + Doxy) showed a significantly better effect than SRP.

Interestingly, by the end of study, intensive OHI showed a better effect than SRP. This may be explained by the fact that OHI is more focused on good oral hygiene habit formation and it shows advantages when the effect of periodontal treatments decreases. As well, SRP combined with oral rinse (CHX rinse; EO-based rinse) appeared to be more effective on plaque control than SRP monotherapy. This is in line CHX rinse's effect on reducing oral bacterial counts and ability of plaque bacteria [77, 78]. Previous systematic reviews have already investigated the long-term effect of mouth rinse containing essential oils on dental plaque, which showed it significantly reduced dental plaque [79].

Gingival index (GI)

SRP showed a significantly better effect than control/no treatment at both assessment times. At 3 months, SRP + Omega 3 + aspirin and SRP + SZ gel were significantly better than SRP. By the end of study, all significant effects attenuated to non-significant. The conclusion should be interpreted with extreme caution for the results were based on limited data.

What is noteworthy is that, compared with SRP monotherapy, the adjunctive use of CHX rinse showed a worse effect on GI. This finding could be seen in both fixed- and random- effects models. Although, there is no direct comparison between CHX rinse and SRP + CHX rinse, the consistency test showed a very strong match between the residuals of the consistency and inconsistency models (Appendix 8). The worse effect might be related to the side effect of CHX rinse on soft tissue [80], but that remains uncertain. More studies are warranted in order to make a clear conclusion.

4.2.3 CORRELATION

SRP had a significantly better effect on improving serum HbA1c than control/no treatment. It was also associated with significantly improved periodontal parameters as compared to control/no treatment. This demonstrates plausibility for periodontal treatments to have an impact on glycemic control through their impact on periodontal health.

The combined treatment (SRP + systematic used Doxy + locally used aPDT + intensive maintenance), that showed a better effect than SRP at 3 months in terms of HbA1c, was not involved in the network meta-analyses for secondary outcomes. Several combination therapies showed a significantly better effect than SRP in terms of secondary outcomes; however, the significant effect was not reserved in terms of HbA1c.

Some combination treatments did not seem to perform better than control/no treatment in terms of both primary and secondary outcomes. This is a bit surprising. We tried to refer to previous reviews on the effectiveness of these periodontal treatments on periodontitis in general (i.e. not specific to patients with DM); however, no network meta-analysis was found. Previous meta-analyses mainly focused on the impact of one or more antimicrobial agents as an adjunct to SRP, relative to SRP monotherapy [74-76]. One possible explanation for this phenomenon is that the complicated geometric network has a low power to detect the differences between treatments. Heterogeneity may also play a role in this.

4.3 CLINICAL IMPORTANCE

With regard to the observed reduction in HbA1c achieving clinical significance, there is no universally accepted minimal clinically important difference (MCID) in HbA1c. Commonly cited MCIDs typically range from -0.4% to -1.0% [81, 82]. The estimated mean percentage reduction in HbA1c with SRP monotherapy relative to control/no treatment were -0.34% (96% CI: -0.64% to -0.04%) and -0.38% (95% CI: -0.70% to -0.08%) at 3 months and end of study, respectively. In both cases, the efficacy of SRP had possible clinical importance, given that the 95% CIs included the value of the MCID (-0.4%) and the MCID was greater than the point estimate. At 3 months, the

difference between “SRP plus systemic doxycycline, aPDT and intensive maintenance” and SRP monotherapy had probable clinical importance (mean difference: -1.96%; 95% CI: -3.83% to -0.13%). Its 95% CI included the value of the MCID (-0.4%) and the point estimate was greater than the MCID estimate.

No references could be found with regard to universally accepted MCIDs in periodontal parameters. We consulted 4 periodontal experts and none of them could provide specific numbers of MCIDs. The reason for this uncertainty lies in that improvement of periodontal status depends largely on disease classification, pathogeny, and severity. We found the following cited MCIDs in the included studies. Six studies calculated their sample size based on PPD. Four (Macedo 2013, Lin 2012, Mendonca 2012, Al-Zahrani 2009) of them used a MCID of 1 mm. Artese 2015 considered a difference of 2 mm in PPD between groups to be clinically meaningful. By contrast, Gilowski 2012 chose a lower MCID of 0.5 mm. Four of the included studies (Tsalikis 2014, Santos 2012, Santos 2013, Santos 2009) calculated their sample size based on CAL. All of them chose a mean difference of at least 1 mm in CAL between groups to be considered as clinically significant. Little information was available about the expected improvement in other periodontal outcomes achieving clinical significance.

If 1mm is chosen as MCID in both PPD and CAL, SRP is definitely not clinically important as compared to control/no treatment. If 0.5mm is used instead in both PPD and CAL, SRP has possible /probable clinical importance relative to control/no treatment. In either way, the difference between other periodontal treatments and SRP can show all forms of clinical importance: definite clinical importance, probable clinical importance, possible clinical importance, and definitely not clinically important.

4.4 SENSITIVITY ANALYSIS

INFLUENCE OF INDUSTRY FUNDING

Sensitivity analyses for influence of industry funding were only performed for HbA1c. When analyzing data from trials that reported having no industry funding, the results were consistent with the primary analysis involving all trials. SRP showed a

significant effect on reducing serum HbA1c at both 3 months and the end of study. At 3 months, one combination treatment (SRP + systematic used Doxy + locally used aPDT + intensive maintenance) showed a significantly better effect than SRP but the effect was no longer retained at the end of study. This may suggest that the funding source may not be a source of bias in some trials of periodontal therapies.

INFLUENCE OF RISK OF BIAS

Sensitivity analyses for risk of bias were only performed for HbA1c. In order to eliminate the potential effect of trials at high risk of bias, we classified trials as being at low, unclear, or high risk based on their score for 4 domains of the Cochrane risk of bias tool (sequence generation, allocation concealment, blinding of subjective outcomes and incomplete data addressed for efficacy outcomes). When we consider only trials that scored low risk or unclear for all of these 4 domains, the findings at end of study were consistent with the findings of previous analysis involving all trials. However, at 3 months, compared to previous analysis, another treatment (SRP + Doxy + intensive maintenance) also showed a significantly better effect than SRP.

The difference in findings between the previous analysis that included all trials and the analysis that included only trials at low risk of bias or unclear suggests that trials at high risk of bias had an influence on our primary findings, and the results should be interpreted with caution. Because of the small number of trials that were assessed as being at low risk of bias, we were unable to perform the network meta-analysis including only trials that were assessed as being at low risk of bias. Additional trials of high quality are needed to more accurately assess the benefit of periodontal therapies on glycemic control in diabetic patients.

INFLUENCE OF LONG TERM USE OF CHX RINSE

Sensitivity analyses for long-term use of CHX rinse were only performed for HbA1c. Two trials (Llambés 2012 /2008 / 2005 for 3 months and Santos 2013 for 2 months) had prescribed CHX rinse for an extended time of period. To eliminate their potential influence, a sensitivity analysis was performed excluding these two trials. The

findings were consistent with the previous analysis involving all included trials at both assessment times. This suggests that the long term use of CHX rinse may not be heavily influential on previous findings.

INFLUENCE OF FMSRP

Traditionally, SRP is divided into 2-4 sessions with a week apart (PMSRP). Some trials reported in their method section that SRP was finished within 36-72 hours (FMSRP). The effect of rapid completed SRP may be different from the traditional one. In order to assess its influence, this sensitivity analysis excluded all trials that reported performing SRP within 72 hours.

Hemoglobin A1C (HbA1c)

By the end of study, the findings were consistent with previous analysis that included all trials. SRP had a significant effect on HbA1c, while other periodontal therapies showed no significant differences with SRP.

At 3 months, results from the sensitivity analysis were not consistent with that from the primary analysis. In our primary analysis that included all trials, we found SRP significantly improved serum HbA1c level. One treatment (SRP + systematic used Doxy + locally used aPDT + intensive maintenance) had a better effect than SRP. When only trials of traditional SRP were considered, no differences were found between any of the periodontal treatments and control/no treatment. Even the effect of SRP was non-significant.

This discrepancy suggests that SRP finished within 72 hours may have an influence on our primary findings. However, the results should be interpreted with caution for lack of high quality studies. Furthermore, direct evidence from 2 trials (Santos 2012; Santos 2009) comparing effect of FMSRP with PMSRP on glycemic control showed no statistical difference between the two. Neither trial is judged as overall being at low risk of bias.

Periodontal pocket depth (PPD)

To better understand the potential influence of FMSRP, sensitivity analyses excluding trials with FMSRP were also performed for the secondary outcomes of PPD and CAL at 3 months.

Except for SRP + TET (topical) that showed a worse PPD outcome than SRP, results of sensitivity analysis were consistent with primary analysis. SRP was significant in both primary and sensitivity analysis.

Clinical attachment level (CAL)

For the outcome of CAL, results of sensitivity analysis were consistent with primary analysis with one exception. SRP + CLM gel showed a significantly better effect than SRP in sensitivity analysis but not in the primary analysis. Compared to control/no treatment, SRP was significant in both primary and sensitivity analysis.

In a summary, existing evidence was insufficient to make a clear cut conclusion regarding the effect of FMSRP on glycemic control. As for the secondary outcome of PPD and CAL, SRP showed a significantly better effect than control/no treatment in both primary and sensitivity analyses.

4.5 SUBGROUP ANALYSIS

Hemoglobin A1C (HbA1c)

Except for one subgroup (age < 65 yr.), results of subgroup network meta-analyses were all consistent with the previous analysis (base case).

For patients less than 65 years old, no differences were found between any periodontal treatments and control/ no treatment at both 3 months and end of study. Even the effect of SRP was non-significant.

Periodontal pocket depth (PPD)

To better understand the influence of age, subgroup analysis (age < 65 yr.) was also performed for PPD and CAL at both assessment times.

Among patients less than 65 year, the effect of SRP on PPD level was non-significant as compared to control/no treatment at both 3 months and end of study. Four combination treatments (SRP/flap surgery+ Tinidazole + Ampicillin; SRP + SZ gel; SRP + AV gel; SRP + CLM gel) had a better effect than SRP at 3 months. By the end of study, SRP was significantly better than supragingival cleaning and 4 treatments (SRP/flap surgery+ Tinidazole + Ampicillin; SRP + SZ gel; SRP + AV gel; SRP + Doxy gel+ intensive maintenance) showed significantly better effect than SRP.

Results derived from the subgroup analysis were inconsistent with the primary analysis, suggesting age may influence the effect of periodontal treatments on PPD.

Clinical attachment level (CAL)

In the subgroup analysis among patients younger than 65 years, the effect of SRP on CAL was non-significant as compared to control/no treatment at both 3 months and end of study. At 3 months, no statistical difference was found between any other periodontal treatments with SRP. By the end of study, 4 treatments (SRP + SDD; SRP + SDD + intensive maintenance; SRP + SZ gel; SRP + Doxy gel+ intensive maintenance) showed a significantly better effect than SRP.

In a summary, among patients less than 65 years, effect of SRP on HbA1c, PPD and CAL was always non-significant as compared to control/no treatment. This is distinct from the primary analysis, in which SRP was associated with a significantly improved outcome in each case. Results from this network meta-analysis suggest age may have an influence on the effect of periodontal treatments and older patients may react better. However, the results should be interpreted with caution giving the limitations of this network meta-analysis. To better understand the potential influence of age, more studies of high quality are warranted.

4.6 MODEL FIT

For several outcomes, the results based on direct evidence and fixed-effects NMA agreed with each other but not with the random-effects NMA. This may be explained by the conceptual and practical difference between the fixed-effects and random-effects

models. The fixed-effect model assumes that the true effect size for all studies is identical and the only reason that effect size varies between studies is sampling error. The random-effects model, by contrast, assumes that there is a normal distribution of population effect sizes. Therefore, under the fixed-effect model the only source of uncertainty is the within-study (sampling) error. Under the random-effects model there is the same source of uncertainty plus an additional source (between-studies variance). It follows that the variance, standard error, and confidence interval for the summary effect will always be larger under the random-effects model than under the fixed-effects model [83]. We checked the consistency of direct and indirect evidence by plotting the mean deviance of the individual data points derived from the inconsistency model against that from the consistency model. The results showed that estimates of treatment effects from direct and indirect evidence were always in agreement (Appendix 8). Based on DIC and total residual deviance, the random-effects model was considered to be a better fit in all NMAs.

4.7 STRENGTHS AND LIMITATIONS

We have performed a comprehensive systematic review. To our knowledge, this is the first network meta-analysis assessing effect of periodontal therapies on both glycemic control and clinical periodontal parameters in patients with DM and periodontitis. Previously published systematic reviews and meta-analyses have grouped all different periodontal therapies into one treatment group, which is compared to control/no treatment group.

A strength of this systematic review is the literature searching. I have a background of dentistry, and with the help of two information specialists, comprehensive search strategies were developed and modified before applying to each database. As well, we also searched the TRIP databases and conducted hand searches of reference list of relevant articles. In order to diminish publication bias, grey literature searches were also performed in Clinicaltrial.gov, University of York--Centre for Reviews as well as Dissemination and National Guideline Clearinghouse. There is no limitation of language and publication date. We have encountered articles written in Chinese, Persian, German

and Hungarian. Each one was reviewed after translation. After the elaborate search, we found a number of studies that were missed by the previous systematic reviews/meta-analyses.

Furthermore, duration of therapy may have an influence on the effect of periodontal therapies. In order to rule out the influence of duration, network meta-analyses were performed at two time points (3 months after treatment and end of study) for each outcome. This is based on the fact that most included trials assessed outcomes every 3 months. It provides longitudinal comparisons between results assessed at shorter and longer period of time.

Our study also 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. Only 3 (Pradeep 2013; Artese 2015; Koçak 2016) out of 49 included trials were assessed as being at overall low risk of bias in the 4 domains that were considered to be most important. In particular, allocation concealment and blinding were not well described, which may have had an impact on the reliability of subjective outcome.

Second, we made some assumptions when combining treatments. We combined treatments that were judged as similar enough from a pharmaceutical perspective. This could increase the heterogeneity among trials and have an influence on the results.

Third, most of the network meta-analyses involved a large number of treatment nodes and a small number of studies in each head to head comparison, which decreased the analytical power.

Fourth, network meta-analysis could not be performed for some subgroups due to lack of data. Even though subgroup analysis could be performed 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.

Finally, publication bias could not be assessed due to lack of data for all outcomes.

4.8 CONCLUSIONS

We found that SRP may reduce the HbA1c level in diabetic patients and thus could be an effective strategy contributing to glycemic control. Compared with SRP, a statistically significantly better effect was only found for one of the investigated treatments (SRP + systematic used Doxy + locally used aPDT + intensive maintenance) at 3 months. By the end of study, no differences were found between SRP and other periodontal therapies. As for secondary outcomes, SRP was associated with significantly improved periodontal outcomes as compared to the control/no treatment condition. This lends credibility to the results for the primary outcome, demonstrating plausibility for periodontal treatments to have an impact on glycemic control through their impact on periodontal health. Many combination treatments showed better effects than SRP and their effects varied by outcome and duration. Sensitivity and subgroup analysis suggested that FMSRP and age may have influences on treatment effects but no clear conclusion could be made. The quality of included studies was generally unclear or poor and the results should be interpreted with caution giving these limitations to the network meta-analysis. Additional high quality studies are needed to better understand the benefits of periodontal therapies among diabetic patients with periodontitis.

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doi: 10.1002/9780470743386.refs.

APPENDIX 1: PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	i
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	ii- iv
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	8-10
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	14
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	14-23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	24
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	195-198
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	24-25
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	25-26
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	25-26
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this	27-29

		was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	31; 34
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	31-34
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	37
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating, which were pre-specified.	36-37
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	38; 39
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	210-227
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	228-251
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	52-167
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	52-167
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	50
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	52-167
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	168-169
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	182-183
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	183
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	v
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APPENDIX 2: DETAILED LITERATURE SEARCH STRATEGY

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to 2015 Nov. 5

1. exp Diabetes Mellitus/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus, Type 1/
2. diabet*.ti,ab.
3. (DM or IDDM or NIDDM or IIDM or MODY or DM1 or DM2 or DM I or DM II).ti,ab.
4. (insulin* adj1 secret* adj1 dysfunc*).ti,ab.
5. (insulin* adj1 resist*).ti,ab.
6. (impaired glucose tolerance or glucose intoleran*).ti,ab.
7. (insulin* depend* or non insulin* depend* or noninsulin* depend*).ti,ab.
8. insulin* defic*.ti,ab.
9. exp Insulin Resistance/
10. exp Hyperglycemia/
11. (hyperglycemi* or hyperglycaemi*).ti,ab.
12. or/1-11
13. Periodontics/
14. periodontal diseases/ or exp gingival diseases/ or exp periodontal atrophy/ or exp periodontitis/
15. (periodont* or periodent* or perident* or paradont* or pericement* or pyorrhea or pyorrhoea).ti,ab.
16. Dental Care/
17. exp dental implantation/
18. exp Dental Prophylaxis/ or exp Subgingival Curettage/
19. Dental Polishing/
20. Crown Lengthening/
21. Oral Medicine/
22. Surgery, Oral/
23. oral surgical procedures/ or Apicoectomy/ or gingivectomy/ or gingivoplasty/ or Guided Tissue Regeneration, Periodontal/
24. exp tooth extraction/
25. exp Preventive Dentistry/
26. Dental Disinfectants/
27. ((dental or oral) adj2 (care or procedure or medicine)).ti,ab.
28. ((dental or oral or tooth or teeth) adj2 implant*).ti,ab.
29. ((root* or tooth or teeth or dental or oral) adj3 (scaling or plann* or planing or polishing)).ti,ab.
30. crown lengthen*.ti,ab.
31. (mucogingiva* adj1 surg*).ti,ab.
32. ((oral or dent* or gingiva*) adj1 flap adj1 (surg* or procedure or operation)).ti,ab.
33. (gingivectom* or gingivoplast*).ti,ab.
34. guided tissue regenerat*.ti,ab.
35. ((tooth or teeth) adj1 extract*).ti,ab.
36. (Oral adj1 instruction*).ti,ab.
37. (prevent* adj2 dent*).ti,ab.
38. (gingiva* adj2 (atroph* or disease* or recession)).ti,ab.
39. oral hygien*.ti,ab.
40. ((oral or dent* or tooth or teeth) adj4 (antimicro* or antibiot* or antibacter* or anti-bacter* or antiinfect* or disinfect*)).ti,ab.
41. ((aPDT or photodynam*) adj4 (oral or dent* or tooth or teeth)).ti,ab.
42. or/13-41
43. 12 and 42
44. Randomized Controlled Trials as Topic/
45. randomized controlled trial/
46. Random Allocation/

47. Double Blind Method/
48. Single Blind Method/
49. clinical trial/
50. clinical trial, phase i.pt.
51. clinical trial, phase ii.pt.
52. clinical trial, phase iii.pt.
53. clinical trial, phase iv.pt.
54. controlled clinical trial.pt.
55. randomized controlled trial.pt.
56. multicenter study.pt.
57. clinical trial.pt.
58. exp Clinical Trials as topic/
59. or/44-58
60. (clinical adj trial\$).tw.
61. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
62. PLACEBOS/
63. placebo\$.tw.
64. randomly allocated.tw.
65. (allocated adj2 random\$).tw.
66. or/60-65
67. 59 or 66
68. case report.tw.
69. letter/
70. historical article/
71. or/68-70
72. 67 not 71
73. 43 and 72

Embase Classic+Embase 1947 to 2015 Nov. 5

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1. diabetes mellitus/ or impaired glucose tolerance/ or insulin dependent diabetes mellitus/ or non insulin dependent diabetes mellitus/
 2. diabet*.ti,ab.
 3. (DM or IDDM or NIDDM or IIDM or MODY or DM1 or DM2 or DM I or DM II).ti,ab.
 4. (insulin* adj1 secret* adj1 dysfunc*).ti,ab.
 5. (insulin* adj1 resist*).ti,ab.
 6. (Impaired glucose tolerance or glucose intoleran*).ti,ab.
 7. (insulin* depend* or non insulin* depend* or noninsulin* depend*).ti,ab.
 8. insulin* defic*.ti,ab.
 9. exp insulin resistance/
 10. exp hyperglycemia/
 11. (hyperglycemi* or hyperglycaemi*).ti,ab.
 12. or/1-11
 13. periodontics/
 14. periodontal disease/
 15. gingiva disease/ or gingiva bleeding/ or exp gingiva overgrowth/ or exp gingivitis/
 16. periodontitis/ or aggressive periodontitis/ or chronic periodontitis/ or periodontal pocket/
 17. (periodont* or periodent* or perident* or paradont* or pericement* or pyorrhea or pyorrhoea).ti,ab.
 18. dental procedure/
 19. dental surgery/ or tooth extraction/
 20. preventive dentistry/ or dental health education/ or mouth hygiene/ or tooth brushing/
 21. tooth implantation/
 22. orthodontics/

23. stomatology/
24. oral surgery/ or gingivectomy/ or gingivoplasty/ or exp orthognathic surgery/ or gingival retraction technique/
25. ((dental or oral) adj2 (care or procedure or medicine)).ti,ab.
26. ((dental or oral or tooth or teeth) adj2 implant*).ti,ab.
27. ((root* or tooth or teeth or dental or oral) adj3 (scaling or plann* or planing or polishing)).ti,ab.
28. crown lengthen*.ti,ab.
29. (mucogingiva* adj1 surg*).ti,ab.
30. ((oral or dent* or gingiva*) adj1 flap adj1 (surg* or procedure or operation)).ti,ab.
31. (gingivectom* or gingivoplast*).ti,ab.
32. guided tissue regenerat*.ti,ab.
33. ((tooth or teeth) adj1 extract*).ti,ab.
34. (Oral adj1 instruction*).ti,ab.
35. (prevent* adj2 dent*).ti,ab.
36. (gingiva* adj2 (atroph* or disease* or recession)).ti,ab.
37. oral hygien*.ti,ab.
38. ((oral or dent* or tooth or teeth) adj4 (antimicro* or antibiot* or antibacter* or anti-bacter* or antiinfect* or disinfect*)).ti,ab.
39. ((aPDT or photodynam*) adj4 (oral or dent* or tooth or teeth)).ti,ab.
40. or/13-39
41. 12 and 40
42. Clinical trial/
43. Randomized controlled trial/
44. Randomization/
45. Single blind procedure/
46. Double blind procedure/
47. Crossover procedure/
48. Placebo/
49. Randomi?ed controlled trial\$.tw.
50. Rct.tw.
51. Random allocation.tw.
52. Randomly allocated.tw.
53. Allocated randomly.tw.
54. (allocated adj2 random).tw.
55. Single blind\$.tw.
56. Double blind\$.tw.
57. ((treble or triple) adj blind\$).tw.
58. Placebo\$.tw.
59. Prospective study/
60. or/42-59
61. Case study/
62. Case report.tw.
63. Abstract report/ or letter/
64. or/61-63
65. 60 not 64
66. 41 and 65

EBM Reviews - Cochrane Central Register of Controlled Trials Nov. 2015

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1. exp Diabetes Mellitus/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus, Type 1/
 2. diabet*.ti,ab,kw.
 3. (DM or IDDM or NIDDM or IIDM or MODY or DM1 or DM2 or DM I or DM II).ti,ab,kw.
 4. (insulin* adj1 secret* adj1 dysfunc*).ti,ab,kw.
 5. (insulin* adj1 resist*).ti,ab,kw.

6. (impaired glucose tolerance or glucose intoleran*).ti,ab,kw.
7. (insulin* depend* or non insulin* depend* or noninsulin* depend*).ti,ab,kw.
8. insulin* defic*.ti,ab,kw.
9. exp Insulin Resistance/
10. exp Hyperglycemia/
11. (hyperglycemi* or hyperglycaemi*).ti,ab,kw.
12. or/1-11
13. Periodontics/
14. periodontal diseases/ or exp gingival diseases/ or exp periodontal atrophy/ or exp periodontitis/
15. (periodont* or periodent* or perident* or paradont* or pericement* or pyorrhea or pyorrhoea).ti,ab,kw.
16. Dental Care/
17. exp dental implantation/
18. exp Dental Prophylaxis/ or exp Subgingival Curettage/
19. Dental Polishing/
20. Crown Lengthening/
21. Oral Medicine/
22. Surgery, Oral/
23. oral surgical procedures/ or Apicoectomy/ or gingivectomy/ or gingivoplasty/ or Guided Tissue Regeneration, Periodontal/
24. exp tooth extraction/
25. exp Preventive Dentistry/
26. Dental Disinfectants/
27. ((dental or oral) adj2 (care or procedure or medicine)).ti,ab,kw.
28. ((dental or oral or tooth or teeth) adj2 implant*).ti,ab,kw.
29. ((root* or tooth or teeth or dental or oral) adj3 (scaling or plann* or planing or polishing)).ti,ab,kw.
30. crown lengthen*.ti,ab,kw.
31. (mucogingiva* adj1 surg*).ti,ab,kw.
32. ((oral or dent* or gingiva*) adj1 flap adj1 (surg* or procedure or operation)).ti,ab,kw.
33. (gingivectom* or gingivoplast*).ti,ab,kw.
34. guided tissue regenerat*.ti,ab,kw.
35. ((tooth or teeth) adj1 extract*).ti,ab,kw.
36. (Oral adj1 instruction*).ti,ab,kw.
37. (prevent* adj2 dent*).ti,ab,kw.
38. (gingiva* adj2 (atroph* or disease* or recession)).ti,ab,kw.
39. oral hygien*.ti,ab,kw.
40. ((oral or dent* or tooth or teeth) adj4 (antimicro* or antibiot* or antibacter* or anti-bacter* or antiinfect* or disinfect*)).ti,ab,kw.
41. ((aPDT or photodynam*) adj4 (oral or dent* or tooth or teeth)).ti,ab,kw.
42. or/13-41
43. 12 and 42

PubMed Nov. 5 2015

Search (((Diabetes Mellitus[MeSH Terms] OR Diabetes Mellitus, Type 2[MeSH Terms] OR Diabetes Mellitus, Type 1[MeSH Terms]) OR (diabet*[tw] OR DM[tw] OR IDDM[tw] OR NIDDM[tw] OR IIDM[tw] OR MODY[tw] OR DM1[tw] OR DM2[tw] OR DM I[tw] OR DM II[tw])) OR (insulin secret* AND dysfunc*[tw] OR insulin resist*[tw] OR impaired glucose tolerance[tw] OR glucose intoleran*[tw] OR insulin depend*[tw] OR non insulin depend*[tw] OR noninsulin depend*[tw] OR insulin defic*[tw])) OR (Insulin Resistance[MeSH Terms] OR Hyperglycemia[MeSH Terms]) OR (hyperglycemi*[tw] OR hyperglycaemi*[tw])) AND ((Periodontics[MeSH Terms] OR periodontal diseases[MeSH Terms]) OR (periodont*[tw] OR periodent*[tw] OR perident*[tw] OR paradont*[tw] OR pericement*[tw] OR pyorrhea[tw] OR pyorrhoea[tw]) OR (Dental Care[MeSH Terms] OR dental implantation[MeSH Terms] OR Dental Polishing[MeSH Terms] OR Crown Lengthening[MeSH Terms] OR Oral Medicine[MeSH Terms] OR Surgery, Oral[MeSH Terms] OR oral surgical procedures[MeSH Terms] OR Preventive Dentistry[MeSH Terms] OR Dental Disinfectants[MeSH Terms]) OR

((dental[tw] OR oral[tw]) AND (care[tw] OR procedure[tw] OR medicine[tw])) OR ((dental[tw] OR oral[tw] OR tooth[tw] OR teeth[tw]) AND implant*[tw]) OR ((root*[tw] OR tooth[tw] OR teeth[tw] OR dental[tw] OR oral[tw]) AND (scaling[tw] OR plann*[tw] OR planing[tw] OR polishing[tw])) OR (crown lengthen*[tw] OR mucogingiva* AND surg*[tw]) OR ((oral[tw] OR dental[tw] OR gingiva*[tw]) AND (flap surg*[tw] OR flap procedure[tw] OR flap operation[tw])) OR (gingivectom*[tw] OR gingivoplast*[tw] OR guided tissue regenerat*[tw] OR tooth extract*[tw] OR teeth extract*[tw] OR Oral instruct*[tw] OR prevent* AND dentis*[tw] OR prevent* AND dental*[tw] OR gingiva* AND atroph*[tw] OR gingiva* AND disease*[tw] OR gingiva* AND recession[tw] OR oral hygien*[tw]) OR ((oral[tw] OR dental[tw] OR tooth[tw] OR teeth[tw]) AND (antimicro*[tw] OR antibiot*[tw] OR antibacter*[tw] OR anti-bacter*[tw] OR antiinfect*[tw] OR disinfect*[tw])) OR ((oral[tw] OR dental[tw] OR tooth[tw] OR teeth[tw]) AND (aPDT[tw] OR photodynam*[tw]))) AND publisher[sb]

APPENDIX 3: LIST OF INCLUDED STUDIES

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APPENDIX 5: CHARACTERISTICS OF TRIALS THAT ASSESSED SPECIFIC OUTCOMES

CHARACTERISTICS OF TRIALS THAT ASSESSED HEMOGLOBIN A1C (HBA1C)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Tsalikis 2014 p.972	6 mo	SRP (35)	57.94 (8.22)	6.89 (0.60)	6.96 (1.01)	6.8 (0.87)	NA	NA	chairside test A1CNow + Multitest HbA1c system (Bayer HealthCare, Basel, Switzerland)	Yes
		SRP + Doxy (35)	62.9 (10)	6.70 (0.61)	6.62 (0.55)	6.48 (0.71)	NA	NA		
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29)	53.7 (8.0)	8.99 (1.63)	8.94 (1.71)	9.07 (1.69)	NA	8.40 (1.94)	HbA1c (%) was measured by high-performance liquid chromatography	No
		SRP + MTZ + AMX + intensive maintenance (29)	54.0 (8.2)	8.53 (1.56)	8.60 (2.01)	8.49 (2.17)	NA	8.77 (2.93)		
Raman 2014 p.79	3 mo	intensive OHI (20)	54.6 (6.2)	7.6 (1.5)	7.1 (1.2)	NA	NA	NA	The HbA1c testing is DCCT aligned.	No
		SRP + CHX rinse (20)	57.7 (9.9)	7.8 (1.5)	7.1 (1.2)	NA	NA	NA		
Botero 2013 p.706 (Hincapié 2014 p.89)	9 mo	Supragingival cleaning + AZM (35)	56.14 (11.32)	7.84 (1.92)	8.09 (2.62)	8.04 (2.28)	7.84 (2.11)	NA	NR	Mix
		SRP (37)	58.2 (11.1)	7.88 (1.92)	7.21 (1.70)	7.91 (1.78)	7.63§ (2.33)	NA		
Macedo 2014 p.881	3 mo	SRP + AZM (33)	55.9 (12.6)	8.05 (2.04)	7.20 (1.72)	7.59 (1.87)	7.18§ (1.60)	NA	Serum was analyzed by automated immunoturbidimetric method for the determination of HbA1c.	No
		SRP + Doxy + intensive maintenance (15)	48.1 (9)	8.0 (0.93)	7.8 (1.35)	NA	NA	NA		
Engebretson 2013 p.2523 (Engebretson 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowicz 2014 p. 1227)	6 mo	SRP+ Doxy+ aPDT + intensive maintenance (15)	49.4 (6.8)	8.6 (1.1)	7.6 (0.6)	NA	NA	NA	high performance liquid chromatography	No
		Control/no treatment (257)	57.9 (9.6)	7.78 (1.28)	7.88 (2.08)	7.90 (2.40)	NA	NA		
Engebretson 2013 p.2523 (Engebretson 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowicz 2014 p. 1227)	6 mo	SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	7.84 (1.28)	7.99 (1.92)	8.03 (2.08)	NA	NA	high performance liquid chromatography	No
		Control/no treatment (257)	57.9 (9.6)	7.78 (1.28)	7.88 (2.08)	7.90 (2.40)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Li 2011 p.285	6 mo	Control/no treatment (25)	61.64 (9.6)	8.12 (1.88)	7.54 (1.76)	7.48 (2.05)	NA	NA	NR	No
		Supragingival cleaning (19)	64.21 (5.99)	8.15 (1.97)	7.23 (0.94)	7.14 (1.33)	NA	NA		
		SRP (22)	60.86 (10.22)	7.64 (1.77)	7.44 (1.48)	7.08 (1.15)	NA	NA		
Llambés 2012 p. e562 (Llambés2 008 p.337; Llambés 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	7.51 (1.36)	7.45 (1.29)	NA	NA	NA	high-pressure liquid chromatography	No
		SRP + CHX rinse + Doxy (30)	38 (10)	7.64 (1.81)	7.71 (1.74)	NA	NA	NA		
Chen 2012 p.435	6 mo	Control/no treatment (44)	63.2 (8.51)	7.25 (1.49)	7.59 (1.54)	7.38 (1.57)	NA	NA	NR	No
		SRP + non-intensive maintenance (45)	57.91 (11.35)	7.29 (1.55)	7.43 (1.53)	6.87 (1.12)	NA	NA		
		SRP + intensive maintenance (45)	59.86 (9.48)	7.31 (1.23)	7.30 (1.50)	7.09 (1.34)	NA	NA		
Koromantzos 2011 p. 142 (Koromantzos 2012 p.3; Koromantzos 2014 p. 193)	6 mo	Supragingival cleaning (30)	59.42 (9.8)	7.59 (0.66)	7.41 (0.48)	7.46* (0.72)	NA	NA	high-performance liquid chromatography	No
		SRP + intensive maintenance (30)	59.62 (7.95)	7.87 (0.74)	7.14 (0.54)	7.16* (0.69)	NA	NA		
Pradeep 2013 p.24	9 mo	SRP (19)	NR	6.71 (0.13)	6.68 (0.12)	6.68 (0.13)	6.66 (0.13)	NA	NR	NR
		SRP + SMV gel (19)	NR	6.66 (0.11)	6.64 (0.12)	6.65 (0.12)	6.63 (0.10)	NA		
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19)	53.9 (10.8)	10.4 (2.9)	9.7 (2.9)	9.6 (3.2)	NA	8.9 (2.5)	NR	No
		SRP + CHX (topical) + intensive maintenance (19)	50.3 (9.5)	10.0 (2.41)	9.3 (2.75)	9.9 (2.40)	NA	9.7 (2.54)		
Gilowski 2012 p.763	3 mo	SRP (17)	56.0 (9.0)	6.2 (6.0, 7.8)	6.3 (5.5, 7.3)	NA	NA	NA	turbidimetric inhibition immunoassay (Cobas Integra 400 plus; Roche Diagnostics Polska Sp. z o.o., Warsaw, Poland)	No
		SRP + SDD (17)	57.6 (8.0)	6.7 (6.3, 7.0)	6.7 (6.3, 7.7)	NA	NA	NA		
Moeintag havi 2012 p.31	3 mo	Control/no treatment (18)	NR	8.72 (2.22)	8.97* (1.82)	NA	NA	NA	NR	No
		SRP (22)	NR	8.15 (1.18)	7.41* (1.18)	NA	NA	NA		
Santos 2012 p. 45	12 mo	SRP + intensive maintenance (17)	51.9 (7.8)	8.9 (2.2)	9.3 (1.9)	10.2 (2.9)	NA	10.6 (2.9)	high-performance liquid chromatography	No
(Figueiredo 2014 p. 490)		FM-SRP + intensive maintenance (17)	53.1 (8.1)	9.4 (2.5)	10.1 (2.5)	9.7 (2.0)	NA	10.2 (2.5)		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Engebrets on 2011 p.624	3 mo	SRP (15)	53.8 (2)	8.2 (2.0)	0.15 [†] (1.8)	NA	NA	NA	Measurements of HbA1c and glucose levels were carried out on freshly drawn ethylenediamine tetraacetic acid-anti-coagulated whole blood using an automated affinity chromatography system (BioRad Micromat II, Hercules, CA)	No
		SRP + SDD (15)	53.2 (3)	7.9 (1.9)	-0.43 ^{†*} (1.6)	NA	NA	NA		
		SRP + Doxy (15)	54.4 (2)	7.6 (2.0)	0.35 ^{†*} (0.98)	NA	NA	NA		
Khader 2010 p.741	9mo	OHI (29)	57.1 (6.9)	7.73 (0.87)	NA	7.46* (1.46)	7.49* (1.3)	NA	photometric systems The assay is standardized according to the approved International Federation of Clinical Chemistry (IFCC) reference method, 2002.	No
		FM tooth extraction (29)	55.6 (7.9)	8.64 (1.24)	NA	7.41* (0.72)	7.27* (1.0)	NA		
		SRP (98)	51 (6)	9.56 (2.67)	8.89 (3.37)	8.97 (4.75)	9.87 (3.27)	9.9 (5.15)		
Mubarak 2010 p.158	12 mo	SRP + SDD (93)	48 (5)	9.14 (2.60)	8.87 (2.89)	8.54 (2.80)	9.41 (3.95)	9.74 (4.24)	NR	No
		SRP + intensive maintenance (75)	47 (4)	8.87 (2.51)	9.05 (3.38)	8.58 (4.68)	8.82 [‡] (3.64)	8.9 [‡] (4.59)		
		SRP + SDD + intensive maintenance (80)	43 (6)	9.09 (2.86)	9.14 (2.86)	9.2 (2.50)	9.03 (3.13)	9.78 (3.40)		
Al-Zahrani 2009 p.1568	3 mo	SRP (15)	53.14 (10.91)	8.75 (1.43)	8.22 (0.95)	NA	NA	NA	NR	No
		SRP + Doxy (15)	51.42 (6.24)	8.42 (1.65)	7.71 (1.77)	NA	NA	NA		
		SRP + aPDT (15)	51.92 (7.28)	9.25 (2.71)	8.79 (2.85)	NA	NA	NA		
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18)	53.0 (9.2)	9.2 (1.9)	9.6 (2.0)	10.3 (2.6)	NA	NA	NR	NR
Katagiri 2009 p.308	6 mo	FMSRP + intensive maintenance (18)	52.3 (9.4)	9.1 (2.1)	9.8 (2.3)	9.5 (1.9)	NA	NA	high-performance liquid chromatography (Kyotokagaku Co., Ltd., Kyoto, Japan)	Mix
		Control/no treatment (17)	59.0 (4.8)	6.9 (0.9)	6.9 (1.1)	6.9 (0.8)	NA	NA		
		SRP + TET (topical) + intensive maintenance (32)	60.3 (9.9)	7.2 (0.9)	7.1 (0.9)	7.0 (1.0)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
O'Connell 2008 p.774	3 mo	SRP + intensive maintenance (15)	53.5 (13.6)	10.7 (2.0)	9.8 (2.0)	NA	NA	NA	High-pressure liquid chromatography	No
		SRP + Doxy + intensive maintenance (15)	52.3 (6.3)	11.8 (1.6)	10.3 (2.3)	NA	NA	NA		
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10)	41.6 (NR)	9.49 (1.29)	8.91 (1.24)	8.53 (0.75)	NA	NA	NR	NR
		SRP + TET (topical) + non-intensive maintenance (10)	42.0 (NR)	9.11 (0.93)	8.48 (1.41)	8.50 (0.60)	NA	NA		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	8.5 (1.58)	8.3 (1.84)	NA	NA	NA	NR	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	8.060 (1.48)	7.7 (1.84)	NA	NA	NA		
Rocha 2001 p.204	6 mo	SRP (20)	55.0 (3.6)	13.1 (2.9)	NA	10.8 (2.4)	NA	NA	cation-exchange	No
		SRP + ALN (20)	56.0 (3.5)	11.9 (3.2)	NA	9.4 (1.5)	NA	NA		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	7.87 (2.56)	7.96* (2.65)	8.06* (2.72)	NA	NA	HbA1c was determined by using a latex agglutination inhibition assay and an autoanalyzer (Konelab clinical chemistry analyzers, Thermo Scientific., Milan, Italy)	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	8.17 (2.49)	7.49* (1.83)	7.29* (1.61)	NA	NA		
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15)	NR	8.8 (1.8)	7.6* (1.4)	NA	NA	NA	NR	No
		SRP + AMX+ intensive maintenance (15)	NR	9.5 (2.4)	9.2* (1.6)	NA	NA	NA		
Fu 2006 p.32	3 mo	Doxy (23)	55.10 (12.71)	8.22 (2.16)	7.64 (1.73)	NA	NA	NA	high pressure liquid chromatography	NR
		SRP + Doxy (23)	53.41 (11.60)	8.26 (1.49)	7.49 (1.34)	NA	NA	NA		
Singh 2008 p.38	3 mo	Control /no treatment (15)	NR	8.08 (0.78)	8.15* (0.74)	NA	NA	NA	liquid chromatography method	No
		SRP (15)	NR	7.93 (0.78)	7.33* (0.68)	NA	NA	NA		
		SRP + Doxy (15)	NR	8.33 (0.72)	7.55* (0.66)	NA	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	8.7 (0.65)	8.56* (0.69)	NA	NA	NA	immunoturbidimetry	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	8.75 (0.67)	8.25* (0.72)	NA	NA	NA		
Telgi 2013 p.177	3 mo	Control/no treatment (20)	NR	7.74 (0.59)	7.75 (0.58)	NA	NA	NA	NR	NR
		CHX rinse (20)	NR	7.56 (0.59)	7.31 (0.59)	NA	NA	NA		
		SRP + CHX rinse (20)	NR	7.68 (0.63)	7.10‡ (0.64)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Gay 2014 p.673	3 mo	Control/no treatment (77)	54.0 (10.2)	8.4 (2.0)	8.1 (1.8)	NA	NA	NA	automated boronate affinity assay	No
		SRP (77)	51.5 (9.0)	9.0 (2.3)	8.4 (1.9)	NA	NA	NA		
Artese 2015 p.1	6 mo	Supragingival cleaning (12)	54.4 (5.8)	8.55 (8.26, 11.29)	NA	9.22 (7.01, 10.11)	NA	NA	high-performance liquid chromatography	No
		SRP (12)	52.0 (3.3)	8.58 (6.38, 9.59)	NA	7.87 (6.57, 10.00)	NA	NA		
Gaikwad 2013 p.79	3 mo	SRP (25)	NR	8.06 (1.10)	7.11 (0.99)	NA	NA	NA	NR	NR
		SRP + Doxy (25)	NR	8.38 (0.89)	7.00 (0.76)	NA	NA	NA		
Elwakeel 2015 p.721	6 mo	SRP (NR)	NR	7.59 (0.33)	7.14 (0.42)	7 (0.4)	NA	NA	high-performance liquid chromatography	No
		SRP + Omega 3 + aspirin(NR)	NR	7.6 (0.4)	7.43 (0.37)	6.99 (0.51)	NA	NA		
Ardakani 2014 p.1387	3 mo	SRP (15)	NR	6.44 (0.35)	6.12 (0.28)	NA	NA	NA	NR	NR
		SRP + TET (topical) (15)	NR	6.48 (0.51)	6.15 (0.43)	NA	NA	NA		
Zhang 2013 p. 272	3mo	Control/no treatment (25)	62.7 (10.7)	7.38 (1.30)	7.40* (1.00)	NA	NA	NA	NR	No
		SRP (50)	60.4 (9.77)	7.68 (1.22)	7.55* (1.01)	NA	NA	NA		
Koçak 2016	3 mo	SRP (30)	53.1 (5.1)	6.54 (0.66)	-0.22†* (0.25)	NA	NA	NA	NR	No
		SRP + aPDT (30)	51.7 (5.2)	6.91 (0.79)	-0.41†* (0.19)	NA	NA	NA		
† change from baseline										
§ Authors report no statistical differences between the two groups with no p value provided.										
‡ Statistically significantly different from the control/no treatment group										
* Significantly different when compared between groups										

CHARACTERISTICS OF TRIALS THAT ASSESSED PERIODONTAL POCKET DEPTH (PPD)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Tsalikis 2014 p.972	6 mo	SRP (35)	57.94 (8.22)	3.03 (0.73)	2.29 (0.56)	2.27 (0.57)	NA	NA	NR	Yes
		SRP + Doxy (35)	62.9 (10)	3.01 (0.77)	2.46 (0.52)	2.17 (0.5)	NA	NA		
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29)	53.7 (8.0)	3.6 (0.6)	3* (0.5)	2.9* (0.5)	NA	2.9* (0.6)	Six sites per tooth were measured	No
		SRP + MTZ + AMX + intensive maintenance (29)	54.0 (8.2)	3.6 (0.5)	2.6* (0.2)	2.5* (0.2)	NA	2.5* (0.2)		
Raman 2014 p.79	3 mo	Intensive OHI (20)	54.6 (6.2)	2.29 (0.69)	2.02 (0.71)	NA	NA	NA	NR	No
		SRP + CHX rinse (20)	57.7 (9.9)	2.56 (0.57)	1.76 (0.19)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Al-Nowaise r 2014 p.1203	6 mo	SRP (38)	NR	3.82 (0.86)	2.60 (4.19)	2.42 (1.84)	NA	NA	NR	NR
		SRP + Doxy (38)	NR	3.89 (0.75)	2.67 (1.21)	2.39 (1.21)	NA	NA		
Botero 2013 p.706 (Hincapié 2014 p.89)	9 mo	Supragingival cleaning + AZM (35)	56.14 (11.32)	2.4 (0.6)	2.2 (0.4)	2.2 (0.3)	2.1* (0.3)	NA	NR	Mix
		SRP (37)	58.2 (11.1)	2.6 (0.7)	2.5 (0.5)	2.3 (0.5)	2.2* (0.5)	NA		
		SRP + AZM (33)	55.9 (12.6)	2.7 (0.6)	2.3 (0.6)	2.1 (0.3)	2.1* (0.3)	NA		
Macedo 2014 p.881	3 mo	SRP + Doxy +intensive maintenance (15)	48.1 (9)	2.54 (0.53)	1.92 (0.62)	NA	NA	NA	NR	No
		SRP+ Doxy+ aPDT +intensive maintenance (15)	49.4 (6.8)	2.43 (0.27)	1.82 (0.19)	NA	NA	NA		
Engelbrecht 2013 p.2523 (Engelbrecht 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowski 2014 p. 1227)	6 mo	Control/no treatment (257)	57.9 (9.6)	3.3 (0.7)	3.15 (1.44)	3.14* (1.28)	NA	NA	NR	No
		SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	3.3 (0.6)	2.82 (0.96)	2.78* (0.96)	NA	NA		
Li 2011 p.285	6 mo	Control/no treatment (25)	61.64 (9.6)	2.93 (0.58)	-0.21† (0.34)	-0.20† (0.35)	NA	NA	NR	No
		Supragingival cleaning (19)	64.21 (5.99)	3.43 (0.96)	-0.60†‡ (0.53)	- (0.70†‡ (0.51)	NA	NA		
		SRP (22)	60.86 (10.22)	3.12 (0.71)	-0.65†‡ (0.31)	- (0.71†‡ (0.37)	NA	NA		
Bajaj 2012 p. 276	6 mo	SRP (31)	NR	7.23 (0.69)	5.88* (0.84)	6.06* (0.88)	NA	NA	NR	NR
		SRP + CLM gel (32)	NR	7.29 (0.58)	4.93* (0.39)	5.14* (0.40)	NA	NA		
Llambés 2012 p. e562 (Llambés 2008 p.337; Llambés 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	3.35 (0.66)	2.70 (0.41)	NA	NA	NA	NR	No
		SRP + CHX rinse + Doxy (30)	38 (10)	3.43 (0.64)	2.69 (0.32)	NA	NA	NA		
		Control/no treatment (44)	63.2 (8.51)	2.47 (0.57)	2.38 (0.47)	2.42 (0.50)	NA	NA	NR	No
Chen 2012 p.435	6 mo	SRP + non-intensive maintenance (45)	57.91 (11.35)	2.57 (0.66)	2.20‡ (0.39)	2.10‡ (0.39)	NA	NA		
		SRP + intensive maintenance (45)	59.86 (9.48)	2.66 (0.68)	2.27‡ (0.50)	2.18‡ (0.48)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Lin 2012 p.599	6 mo	SRP (14)	59.0 (6.5)	5.15 (0.52)	3.36 (1.12)	3.13 (1.10)	NA	NA	PD was measured from the free gingival margin to the base of the periodontal pocket using a UNC #15 (HuFriedy, Chicago, IL, USA) periodontal probe. Measurements were taken at six sites per tooth.	No
		SRP + TET gel (14)	56.6 (7.8)	5.13 (0.47)	3.39 (0.91)	3.11 (0.92)	NA	NA		
Pradeep 2013 p.24	9 mo	SRP (19)	NR	7.86 (1.09)	6.38* (1.01)	6.17* (0.93)	6.31* (0.89)	NA	NR	NR
		SRP + SMV gel (19)	NR	8.31 (1.04)	5.52* (0.74)	4.52* (0.99)	4.28* (1.00)	NA		
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19)	53.9 (10.8)	3.7 (0.8)	3.0 (0.5)	2.9 (0.5)	NA	2.9 (0.6)	NR	No
		SRP + CHX (topical) + intensive maintenance (19)	50.3 (9.5)	3.4 (0.5)	2.9 (0.4)	2.9 (0.4)	NA	3.0 (0.4)		
Pradeep 2012 p.1322	6 mo	SRP (22)	NR	8.31 (1.80)	6.92* (1.78)	5.94* (1.77)	NA	NA	NR	NR
		SRP + ALN gel (21)	NR	8.41 (2.41)	5.91* (1.82)	3.85* (1.89)	NA	NA		
Gilowski 2012 p.763	3 mo	SRP (17)	56.0 (9.0)	2.81 (2.53, 3.08)	2.37 (1.99, 2.64)	NA	NA	NA	NR	No
		SRP + SDD (17)	57.6 (8.0)	2.83 (2.44, 3.60)	2.22 (1.82, 2.56)	NA	NA	NA		
Mendonca 2012 p. 368 (Bezerra 2014 p.58)	6 mo	SRP + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	6.0 (0.9)	4.3 (0.7)	4.3 (0.8)	NA	NA	NR	No
		Flap surgery + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	6.1 (1.0)	4.2 (1.0)	4.0 (0.9)	NA	NA		
Moeintaghavi 2012 p.31	3 mo	Control/no treatment (18)	NR	2.06 (0.24)	2.33* (0.3)	NA	NA	NA	PPD was measured from the gingival margin with a Williams' periodontal probe (Hu-Friedy, Chicago, IL, USA)	No
		SRP (22)	NR	2.31 (0.65)	2.21* (0.6)	NA	NA	0		
Santos 2012 p. 45 (Figueiredo 2014 p. 490)	12 mo	SRP + intensive maintenance (17)	51.9 (7.8)	3.6 (0.6)	2.6 (0.8)	2.7 (0.8)	NA	2.7 (0.7)	NR	No
		FM-SRP + intensive maintenance (17)	53.1(8.1)	3.3 (0.9)	2.7 (0.9)	2.7 (0.5)	NA	2.8 (0.5)		
Deo 2010	6 mo	SRP (inferred 10)	NR	5.73 (0.22)	NA	3.19* (0.13)	NA	NA	NR	NR
		SRP + SDD (inferred 10)	NR	5.66 (0.50)	NA	2.60* (0.33)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Mubarak 2010 p.158	12 mo	SRP (98)	51 (6)	4.06 (1.29)	3.2 (1.29)	2.94 (1.58)	3.16 (2.57)	2.69 (2.47)	NR	No
		SRP + SDD (93)	48 (5)	3.9 (1.35)	2.88 (1.45)	3.05 (1.64)	2.82 (2.12)	2.4 (1.93)		
		SRP + intensive maintenance (75)	47 (4)	3.86 (1.56)	2.7† (1.21)	2.74 (1.39)	2.63 (1.91)	2.46 (3.03)		
		SRP + SDD + intensive maintenance (80)	43 (6)	3.92 (1.16)	2.86 (1.34)	2.94 (1.34)	2.99 (1.43)	2.29 (2.41)		
Al-Zahrani 2009 p.1568	3 mo	SRP (15)	53.14 (10.91)	3.24 (0.66)	2.64 (0.70)	NA	NA	NA	NR	No
		SRP + Doxy (15)	51.42 (6.24)	3.26 (0.45)	2.82 (0.23)	NA	NA	NA		
		SRP + aPDT (15)	51.92 (7.28)	3.00 (0.46)	2.55 (0.33)	NA	NA	NA		
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18)	53.0 (9.2)	3.5 (0.6)	2.5 (0.7)	2.8 (0.5)	NA	NA	NR	NR
		FMSRP + intensive maintenance (18)	52.3 (9.4)	3.2 (0.5)	2.4 (0.6)	2.6 (0.3)	NA	NA		
Katagiri 2009 p.308	6 mo	Control/no treatment (17)	59.0 (4.8)	2.8 (0.9)	2.6* (0.7)	2.6* (0.7)	NA	NA	NR	Mix
		SRP + TET (topical) + intensive maintenance (32)	60.3 (9.9)	3.0 (0.9)	2.2* (0.5)	2.2* (0.50)	NA	NA		
O'Conne II 2008 p.774	3 mo	SRP + intensive maintenance (15)	53.5 (13.6)	2.9 (0.8)	2.1* (0.3)	NA	NA	NA	NR	No
		SRP + Doxy + intensive maintenance (15)	52.3 (6.3)	3.0 (0.5)	1.9* (0.3)	NA	NA	NA		
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10)	41.6 (NR)	6.10 (0.51)	4.23 (0.94)	3.92* (1.08)	NA	NA	NR	NR
		SRP + TET (topical) + non-intensive maintenance (10)	42.0 (NR)	5.94 (0.67)	3.51 (0.69)	2.67* (0.42)	NA	NA		
Lima 2004 p.648	12 mo	SRP + intensive maintenance (11)	NA	5.8 (0.99)	NA	3.6 (1.33)	3.8 (1.33)	3.9* (1.33)	The distance from gingival margin to the base of the pocket	No
		SRP + Doxy gel +intensive maintenance (11)	NA	6.0 (0.99)	NA	2.1 (0.66)	2.0 (0.66)	2.0* (0.66)		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	3.65 (0.76)	3.40 (0.71)	NA	NA	NA	NR	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	3.55 (0.82)	3.23 (0.71)	NA	NA	NA		
Rocha 2001 p.204	6 mo	SRP (20)	55.0 (3.6)	3.9 (0.9)	NA	3.1* (0.8)	NA	NA	NR	No
		SRP + ALN (20)	56.0 (3.5)	4.1 (1.0)	NA	2.8* (0.6)	NA	NA		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	3.08 (0.55)	3.10* (0.56)	3.13* (0.57)	NA	NA	defined as the distance from the gingival margin to the base of the clinical pocket	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	2.96 (0.46)	2.17* (0.43)	2.15* (0.42)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15)	NR	3.2 (0.8)	2.3 (0.5)	NA	NA	NA	NR	No
		SRP + AMX + intensive maintenance (15)	NR	2.7 (0.7)	1.9 (0.4)	NA	NA	NA		
Fu 2006 p.32	3 mo	Doxy (23)	55.10 (12.71)	3.77 (0.96)	3.61 (0.34)	NA	NA	NA	NR	NR
		SRP + Doxy (23)	53.41 (11.60)	3.86 (0.62)	3.42 (1.15)	NA	NA	NA		
Singh 2008 p.38	3 mo	Control/no treatment (15)	NR	2.45 (0.26)	2.40 (0.46)	NA	NA	NA	NR	No
		SRP (15)	NR	2.67 (0.36)	2.33 (0.35)	NA	NA	NA		
		SRP + Doxy (15)	NR	2.53 (0.47)	2.15 (0.46)	NA	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	4.49 (0.85)	4.28* (0.81)	NA	NA	NA	NR	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	4.53 (0.83)	2.97* (0.78)	NA	NA	NA		
Telgi 2013 p.177	3 mo	Control/no treatment (20)	NR	5.05 (0.69)	5.03 (0.69)	NA	NA	NA	NR	NR
		CHX rinse (20)	NR	5.11 (0.57)	4.87 (0.55)	NA	NA	NA		
		SRP + CHX rinse (20)	NR	5.05 (0.70)	4.59 (0.72)	NA	NA	NA		
Priyanka 2015 p.42	6 mo	SRP (32)	42.2 (8.2)	8.24 (1.32)	6.55* (1.22)	6.15* (1.11)	NA	NA	NR	NR
		SRP + SZ gel (32)	40.3 (10.2)	8.31 (1.42)	5.32* (1.25)	3.58* (1.22)	NA	NA		
Artese 2015 p.1	6 mo	Supragingival cleaning (12)	54.4 (5.8)	4.47 (3.03, 4.66)	NA	3.30* (2.80, 3.375)	NA	NA	NR	No
		SRP (12)	52.0 (3.3)	4.75 (3.12, 4.96)	NA	2* (2.05, 2.78)	NA	NA		
Gaikwad 2013 p.79	3 mo	SRP (25)	NR	3.34 (0.40)	2.85 (0.20)	NA	NA	NA	NR	NR
		SRP + Doxy (25)	NR	3.36 (0.35)	3.16 (1.54)	NA	NA	NA		
Elwakeel 2015 p.721	6 mo	SRP (NR)	NR	5.85 (0.99)	4.55* (0.83)	3.8* (0.7)	NA	NA	measured from gingival margin until depth of the pocket	No
		SRP + Omega 3 + aspirin(NR)	NR	5.7 (0.8)	3.5* (0.51)	2.8* (0.52)	NA	NA		
Pradeep 2015	6 mo	SRP (30)	34.76 (5.57)	7.27 (0.92)	6.10* (0.99)	5.27* (0.98)	NA	NA	NR	NR
		SRP + AV gel (30)	35.03 (4.78)	7.26 (0.94)	5.43* (0.97)	4.60* (0.93)	NA	NA		
Agarwal 2012	9 mo	SRP (32)	NR	7.27 (0.73)	6.03 (0.90)	5.10* (0.75)	4.51* (1.25)	NA	NR	NR
		SRP + AZM gel (31)	NR	7.38 (0.71)	5.88 (0.94)	4.98* (0.50)	3.96* (0.57)	NA		
Ardakani 2014 p.1387	3 mo	SRP (15)	NR	6.4 (0.45)	5.2* (0.6)	NA	NA	NA	NR	NR
		SRP + TET (topical) (15)	NR	6.52 (0.49)	5.68* (0.43)	NA	NA	NA		

† change from baseline
‡ Statistically significantly different from the control/no treatment group
* Significantly different when compared between groups

CHARACTERISTICS OF TRIALS THAT ASSESSED CLINICAL ATTACHMENT LEVEL (CAL)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Tsalikis 2014 p.972	6 mo	SRP (35)	57.94 (8.22)	3.77 (1.24)	3.16 (1.38)	2.87 (0.89)	NA	NA	NR	Yes
		SRP + Doxy (35)	62.9 (10)	3.73 (0.88)	3.27 (0.77)	3.02 (0.67)	NA	NA		
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29)	53.7 (8.0)	4.6 (0.8)	4.1 (0.8)	4.0 (0.9)	NA	4.1 (0.9)	Six sites per tooth	No
		SRP + MTZ + AMX + intensive maintenance (29)	54.0 (8.2)	4.6 (1.2)	3.8 (0.9)	3.7 (0.9)	NA	3.7 (0.9)		
Raman 2014 p.79	3 mo	intensive OHI (20)	54.6 (6.2)	2.79 (0.96)	2.56 (0.97)	NA	NA	NA	NR	No
		SRP + CHX rinse (20)	57.7 (9.9)	3.35 (0.83)	2.73 (0.70)	NA	NA	NA		
Al-Nowaise r 2014 p.1203	6 mo	SRP (38)	NR	5.31 (1.21)	4.43 (0.92)	4.35 (1.44)	NA	NA	NR	NR
		SRP + Doxy (38)	NR	4.92 (1.01)	4.44 (1.01)	4.18 (1.12)	NA	NA		
Botero 2013 p.706 (Hincapi é 2014 p.89)	9 mo	Supragingival cleaning + AZM (35)	56.14 (11.32)	2.9 (1.1)	2.8 (0.9)	2.8 (0.9)	2.7* (1.0)	NA	NR	Mix
		SRP (37)	58.2 (11.1)	3.1 (1.16)	3.0 (1.1)	3.0 (1.25)	2.8* (1.0)	NA		
		SRP + AZM (33)	55.9 (12.6)	2.8 (0.8)	2.5 (0.8)	2.6 (0.7)	2.6* (0.7)	NA		
Macedo 2014 p.881	3 mo	SRP + Doxy + intensive maintenance (15)	48.1 (9)	3.25 (0.97)	2.79 (0.82)	NA	NA	NA	NR	No
		SRP+ Doxy+ aPDT+ intensive maintenance (15)	49.4 (6.8)	3.39 (0.84)	2.85 (0.71)	NA	NA	NA		
Engelbre tson 2013 p.2523 (Engelbre tson 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowski 2014 p. 1227)	6 mo	Control/no treatment (257)	57.9 (9.6)	3.5 (0.9)	3.42 (1.92)	3.44* (1.76)	NA	NA	NR	No
		SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	3.5 (0.8)	3.16 (1.60)	3.12* (1.44)	NA	NA		
Li 2011 p.285	6 mo	Control/no treatment (25)	61.64 (9.6)	2.26 (1.35)	-0.06† (0.35)	-0.03† (0.28)	NA	NA	NR	No
		Supragingival cleaning (19)	64.21 (5.99)	2.23 (1.16)	- (0.65†‡ (0.40)	-0.86†‡ (0.43)	NA	NA		
		SRP (22)	60.86 (10.22)	2.90 (1.70)	- (0.45†‡ (0.39)	-0.57†‡ (0.46)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Bajaj 2012 p. 276	6 mo	SRP (31)	NR	6.26 (0.31)	5.14* (0.37)	5.72* (0.41)	NA	NA	NR	NR
		SRP + CLM gel (32)	NR	6.32 (0.66)	4.68* (0.47)	4.95* (0.44)	NA	NA		
Llambés 2012 p. e562 (Llambés 2008 p.337; Llambés 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	2.65 (1.25)	2.23 (1.19)	NA	NA	NA	NR	No
		SRP + CHX rinse + Doxy (30)	38 (10)	2.94 (1.31)	2.49 (0.86)	NA	NA	NA		
Chen 2012 p.435	6 mo	Control/no treatment (44)	63.2 (8.51)	3.37 (1.24)	3.29 (1.23)	3.41 (1.23)	NA	NA	NR	No
		SRP + non-intensive maintenance (45)	57.91 (11.35)	2.95 (1.21)	2.55‡ (1.15)	2.55‡ (1.16)	NA	NA		
		SRP + intensive maintenance (45)	59.86 (9.48)	3.57 (1.31)	3.28‡ (1.25)	3.20‡ (0.23)	NA	NA		
Lin 2012 p.599	6 mo	SRP (14)	59.0 (6.5)	5.84 (0.67)	3.78 (0.98)	3.98 (0.90)	NA	NA	distance between the cemento-enamel junction and the bottom of the periodontal pocket; it was measured at six sites around the teeth with the periodontal probe	No
		SRP + TET gel (14)	56.6 (7.8)	5.80 (0.88)	4.15 (0.95)	3.76 (0.81)	NA	NA		
Pradeep 2013 p.24	9 mo	SRP (19)	NR	6.31 (0.81)	5.31* (0.76)	4.93* (0.65)	5.17* (0.71)	NA	NR	NR
		SRP + SMV gel (19)	NR	6.41 (0.87)	3.93* (0.92)	2.59* (0.73)	2.45* (0.83)	NA		
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19)	53.9 (10.8)	4.4 (0.99)	3.9 (0.87)	3.8 (0.92)	NA	3.8 (0.81)	NR	No
		SRP + CHX (topical) + intensive maintenance (19)	50.3 (9.5)	4.1 (0.85)	3.7 (0.92)	3.6 (0.77)	NA	3.9 (0.90)		
Pradeep 2012 p.1322	6 mo	SRP (22)	NR	6.53 (1.87)	5.83* (1.95)	4.92* (1.93)	NA	NA	NR	NR
		SRP + ALN gel (21)	NR	6.24 (1.65)	3.82* (2.08)	2.65* (1.45)	NA	NA		
Gilowski 2012 p.763	3 mo	SRP (17)	56.0 (9.0)	4.19 (3.53, 5.11)	3.99 (2.80, 4.66)	NA	NA	NA	NR	No
		SRP + SDD (17)	57.6 (8.0)	3.79 (3.31, 5.05)	3.16 (2.84, 4.33)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Mendonca 2012 p. 368 (Bezerra 2014 p.58)	6 mo	SRP + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	6.6 (1.1)	5.2 (1.7)	5.3 (1.5)	NA	NA	NR	No
		Flap surgery + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	6.7 (0.9)	5.1 (1.2)	5.3 (1.5)	NA	NA		
Moeintaghavi 2012 p.31	3 mo	Control/no treatment (18)	NR	3.1 (1.05)	3.47* (1.44)	NA	NA	NA	CAL was defined as the distance from the cemento-enamel junction to the bottom of the pocket	No
		SRP (22)	NR	3.14 (1.08)	2.8* (1.09)	NA	NA	NA		
Santos 2012 p. 45 (Figueiredo 2014 p. 490)	12 mo	SRP + intensive maintenance (17)	51.9 (7.8)	4.2 (0.9)	3.5 (0.7)	3.4 (1.2)	NA	3.4 (1.0)	NR	No
		FM-SRP + intensive maintenance (17)	53.1(8.1)	3.8 (0.6)	3.1 (0.7)	3.1 (0.6)	NA	3.2 (0.6)		
Deo 2010	6 mo	SRP (inferred 10)	NR	6.03 (0.45)	NA	4.45* (0.30)	NA	NA	NR	NR
		SRP + SDD (inferred 10)	NR	6.05 (0.25)	NA	3.80* (0.23)	NA	NA		
Mubarak 2010 p.158	12 mo	SRP (98)	51 (6)	5.58 (2.28)	4.92 (2.18)	4.87 (2.47)	4.8 (3.07)	5.25 (2.87)	NR	No
		SRP + SDD (93)	48 (5)	5.01 (1.93)	4.43 (2.22)	4.6 (2.41)	4.47 (2.89)	4.37 (2.41)		
		SRP + intensive maintenance (75)	47 (4)	5.32 (2.34)	4.42 (2.08)	4.53 (2.17)	4.48 (3.55)	4.89 (2.51)		
		SRP + SDD + intensive maintenance (80)	43 (6)	4.96 (1.61)	4.45 (1.70)	4.64 (1.79)	4.65 (1.52)	3.83‡ (1.61)		
Al-Zahrani 2009 p.1568	3 mo	SRP (15)	53.14 (10.91)	4.66 (1.32)	4.10 (1.30)	NA	NA	NA	NR	No
		SRP + Doxy (15)	51.42 (6.24)	3.9 (0.74)	3.41 (0.43)	NA	NA	NA		
		SRP + aPDT (15)	51.92 (7.28)	4.33 (1.15)	3.87 (1.16)	NA	NA	NA		
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18)	53.0 (9.2)	4.2 (0.9)	3.5 (0.7)	3.5 (0.9)	NA	NA	NR	NR
		FMSRP + intensive maintenance (18)	52.3 (9.4)	3.8 (0.7)	3.2 (0.7)	3.2 (0.6)	NA	NA		
O'Connell 2008 p.774	3 mo	SRP + intensive maintenance (15)	53.5 (13.6)	10.2 (1.3)	9.7 (1.4)	NA	NA	NA	NR	No
		SRP + Doxy + intensive maintenance (15)	52.3 (6.3)	10.7 (1.6)	9.8 (1.6)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10)	41.6 (NR)	7.70 (1.26)	6.04* (1.32)	5.78* (1.38)	NA	NA	NR	NR
		SRP + TET (topical) + non-intensive maintenance (10)	42.0 (NR)	6.89 (1.36)	4.55* (1.44)	3.80* (1.30)	NA	NA		
Lima 2004 p.648	12 mo	SRP + intensive maintenance (11)	NA	6.6 (1.66)	NA	5.4 (1.99)	5.6 (1.99)	5.7* (1.66)	The distance from CEJ to the base of the pocket	No
		SRP + Doxy gel + intensive maintenance (11)	NA	7.2 (1.33)	NA	4.1 (1.66)	4.0 (1.33)	4.0* (1.33)		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	4.2 (1.38)	3.98 (1.22)	NA	NA	NA	NR	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	3.8 (1.02)	3.7 (1.22)	NA	NA	NA		
Rocha 2001 p.204	6 mo	SRP (20)	55.0 (3.6)	6.0 (2.1)	NA	5.2* (1.9)	NA	NA	NR	No
		SRP + ALN (20)	56.0 (3.5)	6.66 (1.9)	NA	5.35* (1.5)	NA	NA		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	3.37 (0.61)	3.40* (0.62)	3.44* (0.64)	NA	NA	CAL was defined as the distance from the CEJ to the base of the clinical pocket	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	3.46 (0.53)	2.77* (0.62)	2.75* (0.62)	NA	NA		
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15)	NR	12.5 (1.3)	12.5 (1.4)	NA	NA	NA	NR	No
		SRP + AMX + intensive maintenance (15)	NR	12.3 (1.2)	12.3 (1.2)	NA	NA	NA		
Fu 2006 p.32	3 mo	Doxy (23)	55.10 (12.71)	4.25 (1.10)	4.20 (3.74)	NA	NA	NA	NR	NR
		SRP + Doxy (23)	53.41 (11.60)	4.30 (0.86)	4.11 (0.58)	NA	NA	NA		
Singh 2008 p.38	3 mo	Control/no treatment (15)	NR	2.79 (0.34)	2.83 (0.35)	NA	NA	NA	NR	No
		SRP (15)	NR	3.44 (0.45)	3.14 (0.45)	NA	NA	NA		
		SRP + Doxy (15)	NR	3.23 (0.63)	2.88 (0.61)	NA	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	4.88 (1.39)	4.73* (1.29)	NA	NA	NA	NR	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	4.85 (1.38)	4.12* (0.95)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Priyanka 2015 p.42	6 mo	SRP (32)	42.2 (8.2)	7.63 (1.29)	6.11* (1.22)	5.99* (1.15)	NA	NA	Distance from then stent to the base of the pocket minus the distance from the stent to the cemento-enamel junction	NR
		SRP + SZ gel (32)	40.3 (10.2)	7.92 (1.21)	5.42* (1.13)	4.00* (1.11)	NA	NA		
Artese 2015 p.1	6 mo	Supragingival cleaning (12)	54.4 (5.8)	4.77 (3.94, 5.64)	NA	4.26* (3.46, 4.99)	NA	NA	NR	No
		SRP (12)	52.0 (3.3)	4.29 (3.67, 5.13)	NA	3.31* (2.94, 4.18)	NA	NA		
Gaikwad 2013 p.79	3 mo	SRP (25)	NR	3.46 (0.56)	3.03 (0.51)	NA	NA	NA	NR	NR
		SRP + Doxy (25)	NR	3.62 (0.50)	2.96 (0.45)	NA	NA	NA		
Elwakeel 2015 p.721	6 mo	SRP (NR)	NR	6.6 (1.19)	5.1* (0.85)	4.2* (0.52)	NA	NA	measure from depth of the pocket to the cemento-enamel junction	No
		SRP + Omega 3 + aspirin(NR)	NR	6.05 (1.76)	4.15* (1.53)	3* (1.78)	NA	NA		
Pradeep 2015	6 mo	SRP (30)	34.76 (5.57)	6.17 (0.91)	5.37* (0.99)	5.10* (0.92)	NA	NA	NR	NR
		SRP + AV gel (30)	35.03 (4.78)	6.23 (0.89)	5.17* (0.87)	4.57* (0.89)	NA	NA		
Agarwal 2012	9 mo	SRP (32)	NR	6.42 (0.76)	5.38 (0.67)	5.01* (0.56)	4.38* (0.74)	NA	NR	NR
		SRP + AZM gel (31)	NR	6.40 (0.80)	5.17 (0.81)	4.59* (0.58)	3.76* (0.65)	NA		
Zhang 2013 p. 272	3mo	Control/no treatment (25)	62.7 (10.7)	3.33 (0.97)	3.48* (0.97)	NA	NA	NA	NR	No
		SRP (50)	60.4 (9.77)	3.41 (0.97)	2.91* (0.96)	NA	NA	NA		
† change from baseline										
‡ Statistically significantly different from the control/no treatment group										
* Significantly different when compared between groups										

CHARACTERISTICS OF TRIALS THAT ASSESSED BLEEDING ON PROBING (BOP)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Tsalikis 2014 p.972	6 mo	SRP (35)	57.94 (8.22)	36 (28)	11 (1)	12 (12)	NA	NA	NR	Yes
		SRP + Doxy (35)	62.9 (10)	48 (39)	11 (19)	12 (16)	NA	NA		
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29)	53.7 (8.0)	34.2 (15.9)	17.0* (7.9)	16.3* (9.9)	NA	16.9* (10.0)	Percentage of sites with bleeding on probing	No
		SRP + MTZ + AMX + intensive maintenance (29)	54.0 (8.2)	40.7 (14.0)	9.7* (4.9)	9.4* (5.2)	NA	10.6* (5.7)		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Raman 2014 p.79	3 mo	Intensive OHI (20)	54.6 (6.2)	21.6 (15.2)	14.9 (46.3)	NA	NA	NA	NR	No
		SRP + CHX rinse (20)	57.7 (9.9)	20.8 (21.1)	1.8 (1.7)	NA	NA	NA		
Al-Nowaiser 2014 p.1203	6 mo	SRP (38)	NR	63 (33.3)	24 (53.4)	23 (37.9)	NA	NA	NR	NR
		SRP + Doxy (38)	NR	66 (40.8)	27 (56.2)	19 (31.4)	NA	NA		
Botero 2013 p.706 (Hincapié 2014 p.89)	9 mo	Supragingival cleaning + AZM (35)	56.14 (11.32)	43.8 (24.1)	29.1 (17.1)	30.8 (17.8)	29.6 (15.7)	NA	Percentage of sites with bleeding on probing	Mix
		SRP (37)	58.2 (11.1)	45.7 (27.8)	34.1 (20.4)	27.8 (18.3)	24.8 (20.4)	NA		
		SRP + AZM (33)	55.9 (12.6)	52.4 (26.0)	29.2 (17.1)	25.5 (16.5)	28.8 (19.7)	NA		
Macedo 2014 p.881	3 mo	SRP + Doxy + intensive maintenance (15)	48.1 (9)	64.5 (12.5)	15.7 (7.5)	NA	NA	NA	BOP was assessed simultaneously with the pocket measurements, and the presence or absence of bleeding up to 30 s after probing was recorded	No
		SRP+ Doxy+ aPDT + intensive maintenance (15)	49.4 (6.8)	60.4 (12.2)	14.7 (12)	NA	NA	NA		
Engebretson 2013 p.2523 (Engebretson 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowicz 2014 p. 1227)	6 mo	Control/no treatment (257)	57.9 (9.6)	59.3 (25.9)	57 (49.3)	55* (50.6)	NA	NA	six locations around each tooth	No
		SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	60.6 (24.0)	40 (43.0)	40* (40.6)	NA	NA		
Li 2011 p.285	6 mo	Control/no treatment (25)	61.64 (9.6)	2.12 (0.58)	-0.40† (0.43)	-0.42† (0.44)	NA	NA	NR	No
		Supragingival cleaning (19)	64.21 (5.99)	2.24 (0.40)	-0.81†‡ (0.42)	- (0.80†‡ (0.29)	NA	NA		
		SRP (22)	60.86 (10.22)	2.23 (0.64)	-0.89†‡ (0.52)	- (1.00†‡ (0.55)	NA	NA		
Bajaj 2012 p. 276	6 mo	SRP (31)	NR	2.86 (0.23)	1.59* (0.39)	1.51 (0.40)	NA	NA	modified sulcus bleeding index (mSBI)	NR
		SRP + CLM gel (32)	NR	2.95 (0.36)	1.44* (0.16)	1.40 (0.16)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Llambés 2012 p. e562 (Llambés2008 p.337; Llambe's 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	66 (17)	36* (20)	NA	NA	NA	Percentage of sites with bleeding on probing	No
		SRP + CHX rinse + Doxy (30)	38 (10)	65 (17)	27* (14)	NA	NA	NA		
Chen 2012 p.435	6 mo	Control/no treatment (44)	63.2 (8.51)	34.0 (18.9)	28.5 (14.4)	28.4 (13.5)	NA	NA	NR	No
		SRP + non-intensive maintenance (45)	57.91 (11.35)	32.42 (16.63)	12.13‡ (8.24)	12.02‡ (8.99)	NA	NA		
		SRP + intensive maintenance (45)	59.86 (9.48)	37.7 (20.0)	13.4‡ (10.8)	13.9‡ (11.0)	NA	NA		
Lin 2012 p.599	6 mo	SRP (14)	59.0 (6.5)	36.43 (19.58)	15.6 (14.5)	15.9 (14.2)	NA	NA	BOP was measured as a binary variable (yes versus no) for each site, and then a summary score presented as the percentage of sites with bleeding was calculated for each patient	No
		SRP + TET gel (14)	56.6 (7.8)	45.0 (11.7)	11.5 (8.4)	12.7 (7.2)	NA	NA		
Koromant zos 2011 p. 142 (Koromant zos 2012 p.3; Koromant zos 2014 p. 193)	6 mo	Supragingival cleaning (30)	59.42 (9.8)	69.27 (25.9)	NA	- 4.35+* (16.1)	NA	NA	Percentage of sites with presence of bleeding after light mechanical stimulation by a periodontal probe	No
		SRP + intensive maintenance (30)	59.62 (7.95)	71.55 (27.0)	NA	- 38.12+* (22.5)	NA	NA		
Pradeep 2013 p.24	9 mo	SRP (19)	NR	2.81 (0.38)	1.69* (0.17)	1.71* (0.17)	2.06* (0.26)	NA	modified sulcus bleeding index (mSBI)	NR
		SRP + SMV gel (19)	NR	2.98 (0.27)	1.55* (0.30)	1.25* (0.18)	1.32* (0.20)	NA		
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19)	53.9 (10.8)	31.3 (22.4)	15.7 (11.3)	10.7 (9.9)	NA	10.5 (7.5)	NR	No
		SRP + CHX (topical) + intensive maintenance (19)	50.3 (9.5)	33.9 (18.2)	17.4 (14.9)	14.5 (11.9)	NA	16.7 (14.6)		
Pradeep 2012 p.1322	6 mo	SRP (22)	NR	2.71 (0.62)	1.34* (0.91)	1.57* (0.80)	NA	NA	modified sulcus bleeding index (mSBI)	NR
		SRP + ALN gel (21)	NR	2.77 (0.59)	0.99* (0.37)	0.89* (0.94)	NA	NA		
Gilowski 2012 p.763	3 mo	SRP (17)	56.0 (9.0)	30.8 (15.0, 35.7)	20.5 (6.9, 23.2)	NA	NA	NA	NR	No
		SRP + SDD (17)	57.6 (8.0)	37.5 (31.3, 62.5)	14.4 (7.2, 36.4)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Santos 2012 p. 45	12 mo	SRP + intensive maintenance (17)	51.9 (7.8)	53.9 (36.3)	10.9 (10.8)	10.2 (12.2)	NA	9.9 (11.7)	Clinical parameters registered dichotomously [e.g. bleeding on probing (BoP)] were calculated using the Kappa-Light test	No
(Figueiredo 2014 p. 490)		FM-SRP + intensive maintenance (17)	53.1(8.1)	47.3 (26.0)	8.5 (7.1)	6.7 (10.4)	NA	5.0 (5.2)		
Mubarak 2010 p.158	12 mo	SRP (98)	51 (6)	75.8 (32.7)	35.2 (44.6)	31.2 (52.5)	34.8 (57.4)	5.25 (59.4)	NR	No
		SRP + SDD (93)	48 (5)	75.0 (32.8)	24.1 (40.5)	31.2 (43.4)	28 (52.1)	15.9 (61.7)		
		SRP + intensive maintenance (75)	47 (4)	61.7 (41.6)	21.9 (33.8)	21.4 (36.4)	24.3 (55.4)	20.9 (72.7)		
		SRP + SDD + intensive maintenance (80)	43 (6)	65.2 (42.0)	32.5 (47.4)	24.6 (37.6)	28.4 (52.8)	15.1 (54.6)		
Al-Zahrani 2009 p.1568	3 mo	SRP (15)	53.14 (10.91)	72 (24)	43 (28)	NA	NA	NA	NR	No
		SRP + Doxy (15)	51.42 (6.24)	87 (10)	62 (31)	NA	NA	NA		
		SRP + aPDT (15)	51.92 (7.28)	72 (24)	54 (39)	NA	NA	NA		
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18)	53.0 (9.2)	53.0 (36.0)	11.9 (10.2)	11.4 (12.1)	NA	NA	Presence or absence of bleeding up to 15 seconds after gentle probing	NR
		FMSRP + intensive maintenance (18)	52.3 (9.4)	53.8 (26.1)	8.9 (8.2)	8.0 (10.9)	NA	NA		
Katagiri 2009 p.308	6 mo	Control/no treatment (17)	59.0 (4.8)	24.9 (14.7)	20.1* (17.1)	18.8* (18.1)	NA	NA	NR	Mix
		SRP + TET (topical) + intensive maintenance (32)	60.3 (9.9)	36.5 (22.5)	13.4* (12.5)	12.0* (11.4)	NA	NA		
O'Connell 2008 p.774	3 mo	SRP + intensive maintenance (15)	53.5 (13.6)	49.1 (18.5)	14.2 (12.5)	NA	NA	NA	NR	No
		SRP + Doxy + intensive maintenance (15)	52.3 (6.3)	51.3 (14.9)	8.9 (4.8)	NA	NA	NA		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	69.4 (33.1)	48.5* (14.8)	NA	NA	NA	NR	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	63.8 (32.7)	36.1* (15.1)	NA	NA	NA		
Rocha 2001 p.204	6 mo	SRP (20)	55.0 (3.6)	87 (17)	NA	47* (21)	NA	NA	0=absent, 1=present	No
		SRP + ALN (20)	56.0 (3.5)	84 (19)	NA	27* (15)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	75.4 (10.5)	77.0* (11.3)	78.9* (11.8)	NA	NA	Bleeding on probing (BOP) was recorded as present (score 1) if it occurred within 30 s of probing and absent (score 0) if no bleeding occurred	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	73.7 (14.6)	39.1* (11.7)	39.0* (11.6)	NA	NA		
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15)	NR	32 (15)	11 (7)	NA	NA	NA	absent (0), present (1)	No
		SRP + AMX + intensive maintenance (15)	NR	38 (13)	15 (9)	NA	NA	NA		
Fu 2006 p.32	3 mo	Doxy (23)	55.10 (12.71)	70.7 (32.5)	58.2* (18.5)	NA	NA	NA	NR	NR
		SRP + Doxy (23)	53.41 (11.60)	71.5 (25.3)	42.5* (14.4)	NA	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	2.97 (0.66)	2.86* (0.64)	NA	NA	NA	NR	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	2.98 (0.67)	1.92* (0.49)	NA	NA	NA		
Artese 2015 p.1	6 mo	Supragingival cleaning (12)	54.4 (5.8)	73.2 (55.4, 83.9)	NA	42.09* (23.8, 49.4)	NA	NA	absent=0 present=1	No
		SRP (12)	52.0 (3.3)	60.7 (47.4, 69.07)	NA	10.7* (6.07, 20.2)	NA	NA		
Pradeep 2015	6 mo	SRP (30)	34.76 (5.57)	2.9 (0.4)	2.23* (0.67)	1.73* (0.58)	NA	NA	mSBI: modified sulcus bleeding index	NR
		SRP + AV gel (30)	35.03 (4.78)	2.93 (0.25)	1.70* (0.53)	1.57* (0.5)	NA	NA		
Alshehri 2015 p.1	3 mo	SRP (30)	53.4 (2.1)	55.6 (5.3)	11.6* (7.2)	NA	NA	NA	NR	No
		SRP + EO-based rinse (30)	54.2 (3.5)	58.7 (2.1)	3.5* (0.4)	NA	NA	NA		
Agarwal 2012	9 mo	SRP (32)	NR	2.97 (0.32)	2.20 (0.59)	1.73* (0.64)	1.59* (0.58)	NA	mSBI: modified sulcus bleeding index---Loe 1964	NR
		SRP + AZM gel (31)	NR	2.98 (0.56)	1.77 (0.46)	1.63* (0.58)	1.21* (0.36)	NA		
Zhang 2013 p. 272	3mo	Control/no treatment (25)	62.7 (10.7)	52.8 (15.0)	50.9* (16.6)	NA	NA	NA	NR	No
		SRP (50)	60.4 (9.77)	55.7 (16.5)	24.5* (10.5)	NA	NA	NA		

† change from baseline
‡ Statistically significantly different from the control/no treatment group
* Significantly different when compared between groups

CHARACTERISTICS OF TRIALS THAT ASSESSED PLAQUE INDEX (PI)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Miranda 2014 p.890	12 mo	SRP + intensive maintenance (29)	53.7 (8.0)	76.6 (22.2)	32.2 (17.2)	26.5 (16.2)	NA	32.9 (18.5)	Percentage of sites with plaque accumulation	No
		SRP + MTZ + AMX + intensive maintenance (29)	54.0 (8.2)	77.8 (21.0)	30.2 (17.5)	26.8 (15.6)	NA	32.0 (12.6)		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Raman 2014 p.79	3 mo	intensive OHI (20)	54.6 (6.2)	32.7 (21.08)	4.88 (5.88)	NA	NA	NA	NR	No
		SRP + CHX rinse (20)	57.7 (9.9)	40.06 (22.44)	1.96 (5.97)	NA	NA	NA		
Al-Nowaiser 2014 p.1203	6 mo	SRP (38)	NR	2.18 (0.69)	1.47 (1.21)	1.33 (1.21)	NA	NA	NR	NR
		SRP + Doxy (38)	NR	2.14 (0.95)	1.42 (0.77)	1.39 (0.71)	NA	NA		
Botero 2013 p.706 (Hincapié 2014 p.89)	9 mo	Supragingival cleaning + AZM (35)	56.14 (11.32)	58.6 (19.5)	45.0 (20.0)	41.1 (16.4)	47.2 (18.7)	NA	Percentage of surfaces with plaque accumulation	Mix
		SRP (37)	58.2 (11.1)	54.4 (19.1)	39.53 (16.7)	40.3 (20.9)	39.9 (20.8)	NA		
		SRP + AZM (33)	55.9 (12.6)	55.1 (14.6)	42 (18.6)	40.4 (18.6)	45.5 (16.9)	NA		
Macedo 2014 p.881	3 mo	SRP + Doxy + intensive maintenance (15)	48.1 (9)	63.72 (16.92)	19.6 (15.5)	NA	NA	NA	The presence or absence of biofilm at four sites per tooth (plaque index [PI])	No
		SRP+ Doxy+ aPDT + intensive maintenance (15)	49.4 (6.8)	50.24 (19.41)	17.6 (11.3)	NA	NA	NA		
Engebretson 2013 p.2523 (Engebretson 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowicz 2014 p. 1227)	6 mo	Control/no treatment (257)	57.9 (9.6)	84.5 (20.8)	80 (47.2)	82* (43.0)	NA	NA	NR	No
		SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	86.8 (17.9)	64 (55.4)	70* (37.5)	NA	NA		
Li 2011 p.285	6 mo	Control/no treatment (25)	61.64 (9.6)	2.24 (0.46)	-0.36† (0.41)	-0.20† (0.37)	NA	NA	NR	No
		Supragingival cleaning (19)	64.21 (5.99)	2.31 (0.40)	0.70†‡ (0.30)	0.62†‡ (0.30)	NA	NA		
		SRP (22)	60.86 (10.22)	2.15 (0.54)	0.75†‡ (0.15)	0.84†‡ (0.42)	NA	NA		
Bajaj 2012 p. 276	6 mo	SRP (31)	NR	4.42 (0.65)	3.26* (0.65)	3.16* (0.56)	NA	NA	NR	NR
		SRP + CLM gel (32)	NR	4.36 (0.67)	3.09* (0.67)	2.77* (0.61)	NA	NA		
Llambés 2012 p. e562 (Llambés 2008 p.337; Llambés 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	59 (20)	21 (13)	NA	NA	NA	O'Leary PI: four areas per tooth and the percentage of sites with plaque	No
		SRP + CHX rinse + Doxy (30)	38 (10)	64 (19)	21 (17)	NA	NA	NA		
Chen 2012 p.435	6 mo	Control/no treatment (44)	63.2 (8.51)	0.93 (0.56)	0.74 (0.40)	0.75 (0.38)	NA	NA	NR	No
		SRP + non-intensive maintenance (45)	57.91 (11.35)	0.74 (0.38)	0.42‡ (0.31)	0.40‡ (0.28)	NA	NA		
		SRP + intensive maintenance (45)	59.86 (9.48)	0.94 (0.42)	0.40‡ (0.25)	0.45‡ (0.27)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Lin 2012 p.599	6 mo	SRP (14)	59.0 (6.5)	47.93 (7.99)	27.07 (7.50)	18.79 (2.94)	NA	NA	For plaque scores (PS), disclosing solution was applied to all tooth surfaces, and the O'Leary Index [29] was recorded.	No
		SRP + TET gel (14)	56.6 (7.8)	42.93 (7.00)	17.86 (6.55)	19.29 (4.48)	NA	NA		
Pradeep 2013 p.24	9 mo	SRP (19)	NR	1.71 (0.32)	1.12 (0.34)	0.67 (0.23)	0.77 (0.30)	NA	Site-specific plaque score	NR
		SRP + SMV gel (19)	NR	1.75 (0.09)	1.05 (0.21)	0.65 (0.18)	0.74 (0.32)	NA		
Santos 2013 p.155	12 mo	SRP + intensive maintenance (19)	53.9 (10.8)	58.8 (23.6)	31.8 (13.9)	27.5 (12.4)	NA	30.0 (15.9)	Percentage of plaque accumulation	No
		SRP + CHX (topical) + intensive maintenance (19)	50.3 (9.5)	65.9 (19.1)	35.0 (13.1)	36.9 (15.0)	NA	34.5 (12.2)		
Pradeep 2012 p.1322	6 mo	SRP (22)	NR	1.63 (0.93)	1.03 (0.52)	0.48 (0.24)	NA	NA	plaque index (scaled from 0 to 3)	NR
Gilowski 2012 p.763	3 mo	SRP + ALN gel (21)	NR	1.70 (0.36)	0.96 (0.42)	0.48 (0.29)	NA	NA	Approximal plaque index	No
		SRP (17)	56.0 (9.0)	75 (50, 100)	63.6 (46.7, 75)	NA	NA	NA		
		SRP + SDD (17)	57.6 (8.0)	90 (50, 100)	50 (23.8, 100)	NA	NA	NA	PI was quantified using the O'Leary index in which the four smooth surfaces of all existing teeth were scored and a percentage of surfaces with plaque was recorded	No
		Control/no treatment (18)	NR	94.44 (6.62)	87* (18.7)	NA	NA	NA		
		SRP (22)	NR	88.9 (17.38)	63.2* (21.1)	NA	NA	NA	Clinical parameters registered dichotomously [e.g. bleeding on probing (BoP)] were calculated using the Kappa-Light test. It can be inferred PI is also registered dichotomously.	No
		SRP + intensive maintenance (17)	51.9 (7.8)	75.4 (28.3)	29.3 (16)	27 (15.7)	NA	27.2 (20.4)		
(Figueiredo 2014 p. 490)		FM-SRP + intensive maintenance (17)	53.1(8.1)	70.9 (31.8)	29.2 (23.8)	29.2 (18.8)	NA	26.5 (19.1)		
Mubarak 2010 p.158	12 mo	SRP (98)	51 (6)	2.51 (0.79)	1.71 (1.39)	1.87 (1.29)	1.95 (1.48)	1.46 (2.08)	NR	No
		SRP + SDD (93)	48 (5)	2.3 (0.96)	1.53 (1.25)	1.82 (1.16)	1.46 (1.54)	1.69 (1.54)		
		SRP + intensive maintenance (75)	47 (4)	2.15 (0.87)	1.5 (1.13)	1.59 (1.39)	1.4‡ (1.56)	1.51 (1.91)		
		SRP + SDD + intensive maintenance (80)	43 (6)	2.11 (0.89)	1.66 (1.16)	1.55‡ (1.16)	1.8 (1.16)	1.64 (1.61)		
Al-Zahrani 2009 p.1568	3 mo	SRP (15)	53.14 (10.91)	86 (14)	59 (17)	NA	NA	NA	NR	No
		SRP + Doxy (15)	51.42 (6.24)	88 (17)	52 (20)	NA	NA	NA		
		SRP + aPDT (15)	51.92 (7.28)	90 (19)	56 (33)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Santos 2009 p.1237	6 mo	SRP + intensive maintenance (18)	53.0 (9.2)	74.1 (31)	26.2 (14.3)	26.2 (16.5)	NA	NA	Presence or absence of plaque along the cervical margin	NR
		FMSRP + intensive maintenance (18)	52.3 (9.4)	70 (31)	33.9 (28.1)	34.2 (23.5)	NA	NA		
O'Connell 2008 p.774	3 mo	SRP + intensive maintenance (15)	53.5 (13.6)	59.7 (18.8)	37.5 (19)	NA	NA	NA	the presence or absence of biofilm at four sites per tooth	No
		SRP + Doxy + intensive maintenance (15)	52.3 (6.3)	69.9 (17.3)	46.1 (14.2)	NA	NA	NA		
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10)	41.6 (NR)	2.1 (0.57)	0.89 (0.50)	0.87 (0.41)	NA	NA	NR	NR
		SRP + TET (topical) + non-intensive maintenance (10)	42.0 (NR)	1.89 (0.45)	1.00 (0.34)	0.91 (0.38)	NA	NA		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	2.51 (0.56)	1.45* (0.56)	NA	NA	NA	NR	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	2.45 (0.59)	0.86* (0.57)	NA	NA	NA		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	1.63 (0.26)	1.65* (0.31)	1.68* (0.34)	NA	NA	Loe 1964	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	1.64 (0.26)	0.29* (0.12)	0.28* (0.09)	NA	NA		
Rodrigues 2003 p.1361	3 mo	SRP + intensive maintenance (15)	NR	68 (20)	51 (7.5)	NA	NA	NA	presence or absence of biofilm	No
		SRP + AMX + intensive maintenance (15)	NR	77 (23)	62 (13)	NA	NA	NA		
Fu 2006 p.32	3 mo	Doxy (23)	55.10 (12.71)	3.16 (0.58)	3.04* (0.62)	NA	NA	NA	NR	NR
		SRP + Doxy (23)	53.41 (11.60)	3.23 (0.86)	1.57* (0.43)	NA	NA	NA		
Singh 2008 p.38	3 mo	Control/no treatment (15)	NR	1.55 (0.34)	1.52 (0.30)	NA	NA	NA	According to Silness and Loe	No
		SRP (15)	NR	1.73 (0.27)	0.83 (0.16)	NA	NA	NA		
		SRP + Doxy (15)	NR	1.75 (0.16)	0.86 (0.13)	NA	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	2.47 (0.70)	2.18* (0.69)	NA	NA	NA	NR	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	2.44 (0.73)	1.43* (0.67)	NA	NA	NA		
Telgi 2013 p.177	3 mo	Control/no treatment (20)	NR	1.89 (0.14)	0.86 (0.04)	NA	NA	NA	Dental plaque by the PI of Silness and Loe	NR
		CHX rinse (20)	NR	1.88 (0.12)	1.30‡ (0.06)	NA	NA	NA		
		SRP + CHX rinse (20)	NR	1.88 (0.12)	1.05‡ (0.04)	NA	NA	NA		
Priyanka 2015 p.42	6 mo	SRP (32)	42.2 (8.2)	2.98 (0.22)	2.62 (0.14)	2.71 (0.25)	NA	NA	Plaque index (Loe 1967)	NR
		SRP + SZ gel (32)	40.3 (10.2)	2.86 (0.17)	2.56 (0.22)	2.68 (0.16)	NA	NA		
Artese 2015 p.1	6 mo	Supragingival cleaning (12)	54.4 (5.8)	87.8 (63.6, 97.02)	NA	43.2 (12.5, 72.60)	NA	NA	VPI: visible plaque index (0) absent (1) present	No
		SRP (12)	52.0 (3.3)	72.6 (59.9, 97.27)	NA	26.6 (7.42, 33.6)	NA	NA		
Gaikwad 2013 p.79	3 mo	SRP (25)	NR	1.91 (0.13)	0.93 (0.09)	NA	NA	NA	Loe 1967	NR
		SRP + Doxy (25)	NR	1.88 (0.08)	0.98 (0.05)	NA	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Pradeep 2015	6 mo	SRP (30)	34.76 (5.57)	2.77 (0.43)	2.10* (0.71)	1.43* (0.62)	NA	NA	plaque index (Loe 1964)	NR
		SRP + AV gel (30)	35.03 (4.78)	2.73 (0.45)	1.67* (0.48)	1.33* (0.60)	NA	NA		
Alshehri 2015 p.1	3 mo	SRP (30)	53.4 (2.1)	60.3 (2.2)	24.8* (3.4)	NA	NA	NA	NR	No
		SRP + EO-based rinse (30)	54.2 (3.5)	62.6 (5.1)	12.2* (2.5)	NA	NA	NA		
Agarwal 2012	9 mo	SRP (32)	NR	4.38 (0.75)	3.76 (0.76)	3.29* (0.66)	3.22* (0.59)	NA	NR	NR
		SRP + AZM gel (31)	NR	4.43 (0.63)	3.63 (0.68)	3.12* (0.62)	2.69* (0.67)	NA		
Ardakani 2014 p.1387	3 mo	SRP (15)	NR	58.33 (22.41)	25.66 (8.63)	NA	NA	NA	NR	NR
		SRP + TET (topical) (15)	NR	69 (18.72)	38.7 (10.4)	NA	NA	NA		
Zhang 2013 p. 272	3mo	Control/no treatment (25)	62.7 (10.7)	1.73 (0.49)	1.64* (0.64)	NA	NA	NA	NR	No
		SRP (50)	60.4 (9.77)	1.78 (0.6)	0.32* (0.17)	NA	NA	NA		

† change from baseline
‡ Statistically significantly different from the control/no treatment group
* Significantly different when compared between groups

CHARACTERISTICS OF TRIALS THAT ASSESSED GINGIVAL INDEX (GI)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Al-Nowaiser 2014 p.1203	6 mo	SRP (38)	NR	2.08 (0.63)	1.36 (1.67)	1.29* (1.32)	NA	NA	NR	NR
		SRP + Doxy (38)	NR	2.12 (0.65)	1.46 (0.65)	1.36* (1.24)	NA	NA		
Engelbreton 2013 p.2523 (Engelbreton 2013 p. 515; Schoenfeld 2014 p. 1065; Michalowicz 2014 p. 1227)	6 mo	Control/no treatment (257)	57.9 (9.6)	1.4 (0.4)	-0.1† (-0.2, 0.0)	-0.1† (-0.2, 0.0)	NA	NA	NR	No
		SRP + CHX rinse + intensive maintenance (257)	56.7 (10.5)	1.4 (0.4)	-0.4† (-0.5, -0.3)	-0.4† (-0.4, -0.3)	NA	NA		
Bajaj 2012 p. 276	6 mo	SRP (31)	NR	1.89 (0.37)	1.44* (0.33)	1.44* (0.37)	NA	NA	Gingival index	NR
		SRP + CLM gel (32)	NR	1.92 (0.37)	1.35* (0.24)	1.17* (0.21)	NA	NA		
Koromantzos 2011 p. 142 (Koromantzos 2012 p.3; Koromantzos 2014 p. 193)	6 mo	Supragingival cleaning (30)	59.42 (9.8)	61.09 (34.07)	NA	- 13.90† * (18.03)	NA	NA	simplified gingival index (GI)	No
		SRP + intensive maintenance (30)	59.62 (7.95)	65.78 (31.99)	NA	- 48.01† * (27.33)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Moeintaghavi 2012 p.31	3 mo	Control/no treatment (18)	NR	1.15 (0.51)	1.723* (0.48)	NA	NA	NA	Gingival status recordings were made for each tooth according to established GI (gingival index) criteria	No
		SRP (22)	NR	1.867 (0.83)	1.24* (1.03)	NA	NA	NA		
Mubarak 2010 p.158	12 mo	SRP (98)	51 (6)	2.38 (0.69)	1.49 (1.19)	1.5 (1.19)	1.78 (1.29)	1.64 (1.98)	Gingival index	No
		SRP + SDD (93)	48 (5)	2.15 (1.06)	1.23 (1.16)	1.55 (0.96)	1.34‡ (1.54)	1.35 (2.03)		
		SRP + intensive maintenance (75)	47 (4)	2.06 (0.95)	1.27 (1.04)	1.39 (1.13)	1.4‡ (1.47)	1.34 (2.17)		
		SRP + SDD + intensive maintenance (80)	43 (6)	2.06 (0.89)	1.47 (1.16)	1.53 (1.07)	1.64 (1.16)	1.27‡ (2.06)		
Skaleric 2004 p.160	6 mo	SRP + non-intensive maintenance (10)	41.6 (NR)	2.24 (0.40)	0.84 (0.22)	0.76 (0.30)	NA	NA	NR	NR
		SRP + TET (topical) + non-intensive maintenance (10)	42.0 (NR)	2.09 (0.48)	0.69 (0.37)	0.60 (0.25)	NA	NA		
Al-Mubarak 2002 p.295	3 mo	SRP (26)	51.5 (14.4)	2.19 (0.41)	1.15* (0.97)	NA	NA	NA	Modified gingival index	Yes
		SRP + powered subgingival water irrigation (26)	51.2 (13.6)	2.09 (0.56)	0.69* (0.51)	NA	NA	NA		
Kaur 2015 p.201	6 mo	Control/no treatment (50)	52.94 (6.03)	1.63 (0.17)	1.70* (0.30)	1.75* (0.32)	NA	NA	Loe 1963	NR
		OHI+ SRP+ intensive maintenance (50)	51.82 (5.85)	1.57 (0.28)	0.66* (0.27)	0.64* (0.26)	NA	NA		
Singh 2008 p.38	3 mo	Control/no treatment (15)	NR	1.64 (0.28)	1.65 (0.29)	NA	NA	NA	According to Loe and Silness	No
		SRP (15)	NR	1.55 (0.31)	0.81 (0.22)	NA	NA	NA		
		SRP + Doxy (15)	NR	1.68 (0.17)	0.94 (0.13)	NA	NA	NA		
Telgi 2013 p.177	3 mo	Control/no treatment (20)	NR	2.22 (1.11)	2.19 (1.08)	NA	NA	NA	GI of Loe and Silnes	NR
		CHX rinse (20)	NR	2.14 (0.32)	1.33* (0.26)	NA	NA	NA		
Priyanka 2015 p.42	6 mo	SRP + CHX rinse (20)	NR	2.16 (0.46)	1.59*‡ (0.18)	NA	NA	NA	gingival index (Glavind and Loe, 1967)	NR
		SRP (32)	42.2 (8.2)	2.66 (0.25)	1.97 (0.23)	1.86 (0.17)	NA	NA		
		SRP + SZ gel (32)	40.3 (10.2)	2.65 (0.23)	1.61 (0.22)	1.44 (0.27)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Gaikwad 2013 p.79	3 mo	SRP (25)	NR	1.90 (0.08)	0.97 (0.10)	NA	NA	NA	Loe 1967	NR
		SRP + Doxy (25)	NR	1.92 (0.06)	1.02 (0.04)	NA	NA	NA		
Elwakeel 2015 p.721	6 mo	SRP (NR)	NR	2.35 (0.49)	1.9* (0.52)	1.2* (0.5)	NA	NA	gingival index (Loe 1963 Periodontal disease in pregnancy I. Prevalence and severity)	No
		SRP + Omega 3 + aspirin(NR)	NR	2.3 (0.6)	0.85* (0.49)	0.35* (0.49)	NA	NA		
Ardakani 2014 p.1387	3 mo	SRP (15)	NR	2.46 (0.51)	1.7 (0.45)	NA	NA	NA	NR	NR
		SRP + TET (topical) (15)	NR	2 (0.37)	1.4 (0.5)	NA	NA	NA		

† change from baseline
‡ Statistically significantly different from the control/no treatment group
* Significantly different when compared between groups

CHARACTERISTICS OF TRIALS THAT ASSESSED C-REACTIVE PROTEIN (CRP)

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Raman 2014 p.79	3 mo	Intensive OHI (20)	54.6 (6.2)	5.6 (5.2)	5.6 (5.3)	NA	NA	NA	Hs-CRP levels were assessed using tests for High sensitivity CRP (hs-CRP)	No
		SRP + CHX rinse (20)	57.7 (9.9)	10.5 (15.8)	7.0 (13.4)	NA	NA	NA		
Llambés 2012 p. e562 (Llambés2008 p.337; Llambe's 2005 p.915)	3 mo	SRP + CHX rinse (30)	33 (8)	1.19 (0.16, 5.4)	0.98 (0.16, 5.4)	NA	NA	NA	Plasma hs-CRP levels were assessed using a kit with specific high-sensitivity methodology in a spectrophotometer according to the manufacturer's instructions.	No
		SRP + CHX rinse + Doxy (30)	38 (10)	1.27 (0.16, 7.6)	1.05 (0.16, 7.8)	NA	NA	NA		
Chen 2012 p.435	6 mo	Control/no treatment (44)	63.2 (8.51)	2.81 (4.05)	2.24 (2.06)	3.16 (5.45)	NA	NA	hs-CRP	No
		SRP + non-intensive maintenance (45)	57.91 (11.35)	3.09 (4.64)	1.96 (1.98)	1.53‡ (1.27)	NA	NA		
Koromantzios 2011 p. 142 (Koromantzios 2012 p.3; Koromantzios 2014 p. 193)	6 mo	SRP + intensive maintenance (45)	59.86 (9.48)	3.21 (4.45)	1.48 (1.00)	1.58‡ (1.31)	NA	NA	hsCRP was analyzed by an automated enzyme-linked immunoassay (ELISA) method.---log hsCRP	No
		Supragingival cleaning (30)	59.42 (9.8)	0.29 (1.37)	0.43 (1.26)	0.37 (1.04)	NA	NA		
		SRP + intensive maintenance (30)	59.62 (7.95)	0.42 (1.04)	0.22 (1.42)	0.08 (1.42)	NA	NA		

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Katagiri 2009 p.308	6 mo	Control/no treatment (17)	59.0 (4.8)	2068 (453, 5145)	858 (311, 4326)	1314 (449, 2734)	NA	NA	Serum hs-CRP was measured using a latex particle-enhanced immunonephelometric method	Mix
		SRP + TET (topical) + intensive maintenance (32)	60.3 (9.9)	713 (280, 2646)	1197 (567, 3248)	1110 (403, 1896)	NA	NA		
Sun 2011 p.1569	3 mo	Control/no treatment (75)	54.23 (10.85)	5.81 (1.23)	5.51* (1.29)	NA	NA	NA	Analyzed by the automatic biochemical analyzer	No
		SRP/flap surgery+ Tinidazole + Ampicillin (82)	55.13 (11.16)	5.87 (1.26)	5.06* (1.20)	NA	NA	NA		
‡ Statistically significantly different from the control/no treatment group										
* Significantly different when compared between groups										

CHARACTERISTICS OF TRIALS THAT ASSESSED GINGIVAL CREVICULAR FLUID (GCF) VOLUME

Trial	Time	Groups (No. randomized)	Age, mean (SD)	Score, Mean (SD)/Median (Lower, Upper Quartile)					Method of measurement	Industry funding
				Baseline	3 Mo	6 Mo	9 Mo	12 Mo		
Gilowski 2012 p.763	3 mo	SRP (17)	56.0 (9.0)	0.85 (0.6, 1.6)	0.9 (0.7, 1.1)	NA	NA	NA	GCF was collected 5 min later with a periopaper (Oraflow Inc., Smithtown, NY, USA) by placing 1 mm into the pocket entrance for 30 s	No
		SRP + SDD (17)	57.6 (8.0)	0.97 (0.8, 1.4)	0.79 (0.4, 1.2)	NA	NA	NA		
Mendonça 2012 p. 368 (Bezerra 2014 p.58)	6 mo	SRP + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	0.39 (0.20)	0.20 (0.10)	0.17 (0.14)	NA	NA	GCF was collected by inserting the strips (Periopaper; Oraflow Inc., Smithtown, NY, USA) approximately 2 mm into the sulcus/pocket for 30 s.	No
		Flap surgery + MTZ + AMX + CHX rinse + non-intensive maintenance (21)	NA	0.36 (0.17)	0.28 (0.16)	0.18 (0.12)	NA	NA		
Santos 2012 p. 45 (Figueiredo 2014 p. 490)	12 mo	SRP + intensive maintenance (17)	51.9 (7.8)	0.58 (0.18)	0.20 (0.17)	0.21 (0.13)	NA	0.21 (0.10)	Gingival crevicular fluid was collected by inserting standard paper strips (Periopaper; Oraflow Inc., Smithtown, NY, USA) to a depth of approximately 2 mm into the sulcus/pocket for 30 s.	No
		FM-SRP + intensive maintenance (17)	53.1 (8.1)	0.60 (0.18)	0.23 (0.11)	0.21 (0.14)	NA	0.20 (0.10)		

APPENDIX 6: RISK OF BIAS ASSESSMENT

Tsalikis 2014	Quote	Judge	comments
Sequence generation	"Randomization was generated using randomization software, (http://www.randomization.com) and the randomization list was kept by one of the authors (LT) until patients were eligible for the study."	Low	Sequence generation was computerized.
Allocation concealment	Same as above	Unclear	It was unclear as to whether the person actually allocating the treatment was unaware of the treatment assignment.
Blinding of self-report outcomes	"The study was designed as double blinded concerning both patients who received antimicrobials or placebo, and the examiners who were not aware of the treatment that the patient had received. Analysis of subgingival samples and gingival crevicular fluid samples was performed by one of the authors (DS) who was also unaware of the treatment that the patient had received (coded samples)."	Unclear	Although the study was double blinded and placebo controlled, the method of blinding was not described (i.e. no description of the placebo used).
Blinding of subjective outcomes	Same as above	Unclear	Same as above
Blinding of Objective outcomes	Same as above	Low	Blinding was sufficient for the assessment of objective outcomes (i.e. objective outcomes were not very likely to be influenced by lacking of blinding).
Incomplete outcome-- efficacy	Withdrawals: Total: 4/70 = 6% Placebo: 0/35 = 0% Doxycycline: 4/35 = 11%	Low	We judged low risk of bias as the completion rate was >80%. There was a differential withdrawal rate between groups but not statistically significant. Missing data appears to have been handled by excluding the withdrawals from all analyses. 2 of the withdrawals occurred after the 3 month time point (fig 2) but the group Ns reported in the outcome tables as well as in table 1 do not include these subjects.
Incomplete outcome-- safety	"Regarding answers to the questionnaire no major adverse effects were reported for both groups. Dizziness and difficulty to swallow was reported by one female participant in the control group. All subjects reported that they were compliant to antibiotic intake."	Unclear	It is unclear as to whether the 4 subjects who withdrew were included in the assessment of "adverse effects". The reason given for the 4 subjects for withdrawal was "unwilling to continue". We don't know if they were unwilling due to treatment tolerance.
Selective reporting	Results were reported for all pre-specified outcomes	Low	Protocol is unavailable but there was a good match between the outcomes described in the methods and results sections. Adverse effect was also reported.
Miranda 2014	Quote	Judge	comments
Sequence generation	"each selected subject received a code number and one of the study coordinators...used a computer-generated table to randomly allocate them into one of the following treatment groups"	Low	computer generated sequence
Allocation concealment	"The same pharmacy ...prepared the antibiotics and placebos. Identical plastic bottles containing the antibiotics or placebos were sent to one of the study coordinators (P.M.D.), who marked the code number of each subject on each bottle, according to the therapy assigned. Allocation concealment was assured by means of sequentially numbered drug containers of identical appearance."	Low	It looks as if the study coordinator had no way of knowing which treatment was in the bottle.

Blinding of self-report outcomes	"On the 14th day of the medication, subjects answered a questionnaire (administered by the assistant) about any self-perceived side effects." "Subjects in the control group received the placebo pills for 14 days." "double blind" "drug containers of identical appearance"	Low	Drug containers were of identical appearance and they also described the number of days the placebo was given.
Blinding of subjective outcomes	"Study personnel, including the examiner (T.S.M.), the two operators, the investigator responsible for the data analysis (M.Fa.) and the participants were blinded to treatment assignment. "	Low	Low is judged considering the concealed assignment, use of placebo and a different examiner from operator.
Blinding of Objective outcomes	Same as above	Low	The outcomes were not very likely to be influenced by lacking of blinding.
Incomplete outcome-- efficacy	"The data were evaluated using intention-to-treat analysis with last observation carried forward." "Fifty-eight subjects entered the study and were randomly assigned to one of the two treatment groups (n=29/group). Two subjects form the control group did not attend the baseline monitoring visit. Therefore, 27 and 29 subjects were evaluated at baseline in the control and test groups, respectively. Four subjects in the control group and two in the test group were lost during the follow up visits." Withdrawals : Total: 8/58=14% Placebo: 6/29=21% Treatment: 2/29 =7%	High	In the control group, lost to follow up was more than 20% and they used ITT with last observation carried forward (LOCF).
Incomplete outcome-- safety	"Six and fourteen subjects from the control and test groups, respectively, reported at least one adverse effect of the placebos/antibiotics use."	Unclear	Reasons for withdrawals were given as "could not be contacted". We don't know if they could not be contacted due to treatment tolerance.
Selective reporting	NR	Low	Protocol is not available but outcomes specified in the methods section were reported. Adverse events were also reported.
Raman 2014	Quote	Judge	comments
Sequence generation	"All subjects were assigned via block randomization to age matched NSPT and OHI groups"	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information with which to make a judgement
Blinding of self-report outcomes	NR	NA	No patient self-reported outcomes
Blinding of subjective outcomes	"One of the limitations of this study is that this randomized clinical trial was not double-blinded. Due to ethical restrictions, we were unable to have a control group without intervention." "As there was only one examiner involved in the study, intra-examiner reliability assessment was executed."	Unclear	Control group did not have intervention during study. Both patients and people who gave the treatments cannot be blinded. We judged unclear because we don't know whether the assessor was the same people who gave the treatments.
Blinding of Objective outcomes	"...this randomized clinical trial was not double-blinded. Due to ethical restrictions, we were unable to have a control group without intervention."	Low	Lacking of blinding was unlikely to have affected the objective outcome of HbA1c.
Incomplete outcome-- efficacy	Withdrawals Total: 8/40 = 20% OHI: 3/20 = 15% OHI + SRP: 5/20 = 25%	Unclear	The study had an 80% completion rate. However, in the treatment group only 75% completed and there was no mention of the handling of missing data. Based on the data from the tables, we inferred that missing subjects were excluded from all analyses including baseline.
Incomplete	NR	NA	No safety outcomes were reported.

outcome--safety			
Selective reporting	NR	High	The study did not report safety outcomes.
Al-Nowaiser 2014	Quote	Judge	comments
Sequence generation	"Randomization of the subjects into treatment and control groups was performed by using computer-generated random codes."	Low	Sequence generation was computer generated.
Allocation concealment	NR	Unclear	Not enough information to make a judgement
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes.
Blinding of subjective outcomes	"Single blinded" "Subjects belonging to the treatment group received an antimicrobial dose of systemic doxycycline, 100 mg per day for 14 days with a loading dose of 200 mg on the first day. The control group received no treatment other than oral hygiene during the study."	Unclear	Study stated that it was single blinded but they did not tell us who was blinded. Since there was no placebo used it looks as if it might be the investigators who was blinded but this is not clarified (method of blinding was not reported).
Blinding of Objective outcomes	NR	NA	No objective outcomes were reported.
Incomplete outcome--efficacy	Patients completing Total: 68/76 = 89% SRP: 33/38 = 87% SRP + doxycycline = 35/68 = 96%	Low	There was no mention of ITT analysis or handling of missing data however the completion rate both overall and in each group was >80% so the risk of bias is judged to be low.
Incomplete outcome--safety	NR	NA	There was no information about safety outcome.
Selective reporting	Outcomes described in the methods section were all reported in the results section. There was no reporting of adverse events.	High	The study did not mention adverse events which are outcomes that should have been reported.
Botero 2013 (Hincapié 2014)	Quote	Judge	comments
Sequence generation	"To achieve a balance between groups at baseline regarding sex, a restricted randomization was performed by use of a computer-generated table with permutations in blocks of four and with stratification by gender by one of the authors independent of the clinical part of the study (JEB)."	Low	Sequence generation was computer generated.
Allocation concealment	"AZ and placebo tablets were identical and were given to patients in an opaque sealed and coded envelope that resulted from the randomization process."	Low	The allocation was done independently and opaque envelopes were used for treatment dispensation (at least as far as the drug treatment was concerned).
Blinding of self-report outcomes	"Both patients and clinicians performing therapy and examination were blind to the type of pharmacological treatment" "Only one patient reported gastrointestinal discomfort in the placebo group with the last tablet." "AZ and placebo tablets were identical and were given to patients in an opaque sealed and coded envelope that resulted from the randomization."	High	Placebo described as identical, However, this would only apply to the drug component of the trial and patients would not have been blinded to the procedure.
Blinding of subjective outcomes	"Both patients and clinicians performing therapy and examination were blind to the type of pharmacological treatment." "AZ and placebo tablets were identical and were given to patients in an opaque sealed and coded envelope that resulted from the randomization."	Unclear	Blinding was described and looks to be sufficient for the drug component. However, dental treatments were different among groups and there was no information about how personnel were blinded of it. It looks as if the assessors were different from the treating dentists but we are not sure.
Blinding of Objective	"Both patients and clinicians performing therapy and examination were blind to the	Low	Lacking of blinding was unlikely to have affected the objective outcome.

outcomes	type of pharmacological treatment"		
Incomplete outcome-- efficacy	"Intention-to-treat analysis was performed." Withdrawals at 9 months: PB-Sca 4/37=11% AZ-pro 4/35=11% AZ-Sca 1/33=3%	Low	Although there was no definition of ITT/handling of missing data, lost to follow up in all three groups were less than 20%.
Incomplete outcome-- safety	"Only 1 patient reported gastrointestinal discomfort in the placebo group with the last tablet."	Unclear	The reasons for withdrawals were given as "could not be contacted" with which is unclear to judge.
Selective reporting	"Overall, patients had a regular/poor control of glycemia. A reduction from 8.0% to 7.2% ($\Delta 0.8\%$; $p < 0.05$) in HbA1C was observed in the AZ-Sca at 9 mo. as compared to the PB-Sca group in which the reduction was from 7.9% to 7.6% ($\Delta 0.3\%$). There was no decrease in HbA1C in the AZ-Pro group over time (Fig. 2)"	High	Variance for HbA1c was not reported in the text. The SD had to be estimated from a graph.
Macedo 2013	Quote	Judge	comments
Sequence generation	"A randomization approach using computer-generated random numbers was employed to assign subjects to one of the following two treatment modalities: scaling and root planning (SRP; N=15) or SRP and aPDT (SRP = aPDT; N=15)."	Low	Randomization was computer generated.
Allocation concealment	NR	Unclear	No description provided
Blinding of self-report outcomes	"All subjects completed the 3-month evaluation period. No adverse effects were reported by any of the subjects."	Unclear	No details about blinding
Blinding of subjective outcomes	"Clinical parameters were recorded by an experienced examiner that used a computerized periodontal probe to perform the periodontal measurements."	Unclear	No details about blinding were provided. We are not told if the examiner was a different dentist that the one who provided treatment.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be affected by blinding.
Incomplete outcome-- efficacy	"All subjects completed the 3-month evaluation period."	Low	No lost to follow up
Incomplete outcome-- safety	"All subjects completed the 3-month evaluation period."	Low	No lost to follow up
Selective reporting	NR	Low	Although there is no protocol, outcomes specified in the methods section were all reported, and adverse event outcomes were available.
Engebretson 2013	Quote	Judge	comments
Sequence generation	"Eligible individuals were randomized using a permuted-block randomization scheme, stratified by clinical site, with block sizes of 2, 4 or 6."	Unclear	Block is not sufficient to judge computerized.
Allocation concealment	NR	Unclear	No description
Blinding of self-report outcomes	"Two weeks after completion of treatment or baseline, the treatment group experienced more soreness/tenderness/pain than the controls (40.2% (102/254) and 28.1% (72/257) respectively; $p < 0.01$ (based on chi-square test), and thermal sensitivity (31.9% (81/254) vs. 18.3% (47/257), respectively ($p < 0.01$ (based on chi-square test)). These symptoms are commonly reported following scaling and root planning. Few participants, (4/241 in the	High	Patients were not blind to dental procedure (control group - delayed treatment).

	treatment group and 5/236 in the control group) required generalized periodontal rescue therapy during the study. “		
Blinding of subjective outcomes	“Periodontal examiners and laboratory personnel who performed the HbA1c analyses were masked to treatment group assignment.” “single-masked”	Unclear	Insufficient information about blinding for subjective outcomes. It is unclear as to whether different personnel were used for treatment and assessment.
Blinding of Objective outcomes	“Periodontal examiners and laboratory personnel who performed the HbA1c analyses were masked to treatment group assignment.”	Low	Objective outcomes were unlikely to be affected by lacking of blinding.
Incomplete outcome--efficacy	“The primary outcome, change in HbA1c, was analyzed using the intention-to-treat principle using linear extrapolation with multiple imputation to impute missing 6-month HbA1c values.” “The secondary efficacy analysis... a “per protocol” analysis based on data available both at baseline and the 6-month visit, was also performed without imputation” “Of the 514 participants randomized, 476 (93%) completed the study, with similar retention in the treatment (240/257) and control (236/257) groups.”	Low	The total lost to follow up was less than 20% and there was no significant difference between groups.
Incomplete outcome--safety	“Of the 514 participants randomized, 476 (93%) completed the study, with similar retention in the treatment (240/257) and control (236/257) groups”	Unclear	The reasons for lost to follow up were unclear. We don't know if withdrawals might have been due to an adverse event.
Selective reporting	NR	High	Data of HbA1c had to be extracted from a graph.
Li 2011	Quote	Judge	comments
Sequence generation	The random number was generated by SAS 8.0.	Low	Randomization was computer generated.
Allocation concealment	NR	Unclear	No description
Blinding of self-report outcomes	NR	NA	No patient self-reported outcomes
Blinding of subjective outcomes	...examiner was blinded	Unclear	Insufficient information about blinding
Blinding of Objective outcomes	...examiner was blinded	Low	Objective outcomes were not likely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	NR	Unclear	This article did not report number of lost to follow up and the statistic method they used.
Incomplete outcome--safety	NR	NA	No safety outcomes were reported
Selective reporting	NR	High	The article did not report any safety outcome.
Bajaj 2012	Quote	Judge	comments
Sequence generation	“After subject enrollment by an examiner (ARP), subjects were randomly assigned (by computer generated system) to...”	Low	Sequence was computer generated.
Allocation concealment	“Subjects were blinded for allocation...”	Unclear	Insufficient information to judge
Blinding of self-report outcomes	“Subjects were blinded for allocation...” “No adverse reaction was observed in any subject from the test group, and no patient reported any discomfort.” “double blinded, placebo controlled”	Unclear	There was insufficient information about blinding and the placebo gel was not well described.
Blinding of subjective	“All pre- and post-treatment clinical parameters were recorded by an examiner	Low	Although there was insufficient information about blinding, the examiner was not the same

outcomes	(ARP) who was masked to the type of treatment received by the subjects, while another clinician (PB) provided treatment to both groups." "double blind"		person who performed the treatments.
Blinding of Objective outcomes	NR	NA	No objective outcomes
Incomplete outcome--efficacy	Subjects completing : SRP + Placebo: 27/31 = 87% SRP + CLM: 29/32 = 90%	Low	The total lost to follow up was less than 20% and was balanced between the two arms.
Incomplete outcome--safety	NR	Unclear	The reasons for lost to follow up were unclear and we do not know if the subjects who "failed to follow up" were assessed for adverse events.
Selective reporting	NR	Unclear	Outcomes were not pre-specified in the methods section. Incomplete reporting of adverse events. It is unclear as to which adverse events were assessed.
Llambés 2012 (Llambés2008; Llambe's 2005)	Quote	Judge	comments
Sequence generation	"The sample was randomized, allowing the subjects to self-select a coded number contained in an envelope; this number identified the group to which the patient was assigned (group 1 or 2)" In the companion article: "When a patient dropped out of the study, a new patient that matched the selection criteria was included in order to maintain the sample size which consisted of 30 patients in each group. In the present study, 12 patients dropped out and were replaced by 12 new patients."	Unclear	It was not clear how the sequence was generated.
Allocation concealment	Same as above	High	When a patient dropped out, a new patient was selected. This would break the concealment.
Blinding of self-report outcomes	NR	NA	There are no patient self-reported outcomes.
Blinding of subjective outcomes	"This clinician was blinded to the treatment applied in each patient and care was taken that subjects did not disclose their group category" In the companion article: "This clinician was blinded to the treatment applied in each patient and care was taken that subjects did not disclose their group category" "...this single-blind study"	Unclear	Although effort was made to blind the outcome assessors, the trial was not placebo controlled therefore it may have been difficult to maintain this blinding.
Blinding of Objective outcomes	"This clinician was blinded to the treatment applied in each patient and care was taken that subjects did not disclose their group category" "...this single-blind study"	Low	No details about blinding but outcomes were unlikely to be influenced.
Incomplete outcome--efficacy	"At the end of the study, 19 subjects were dropped out." "Nine patients did not follow post-operative anti-infectious treatment (chlorhexidine rinses and doxycycline if prescribed), 3 subjects had active acute infections during post-treatment period and 7 patients had an inadequate baseline laboratory exam (high-sensitivity C-reactive protein test could not be performed). Finally, baseline hs-CRP could be obtained from 53 patients and post-treatment hs-CRP was measured in 47 individuals (24 patients from group 1 and 23 patients from group 2)." In the companion article: "72 were found to match the selection criteria" At the end of the study, 12 subjects were	High	Over 20% patients withdrew from the study. Based on the table, it is inferred they used the per-protocol analysis. Reasons for withdrawals were not reported by study group. The randomized number of patients in each group was not reported.

	dropped out because they did not follow appropriately the study protocol or due to active acute infections during posttreatment period. Finally, 30 patients remained in group 1 and 30 patients in group 2.” “When a patient dropped out of the study, a new patient that matched the selection criteria was included in order to maintain the sample size which consisted of 30 patients in each group. In the present study, 12 patients dropped out and were replaced by 12 new patients.”		
Incomplete outcome--safety	“...3 subjects had active acute infections during post-treatment period”	NA	No safety outcomes with usable data were reported.
Selective reporting	NR	High	They did not break down withdrawals by group. As well, the number of acute infections was reported but not broken down by group so was not usable.
Chen 2012	Quote	Judge	comments
Sequence generation	“a computer-generated list of random numbers was used”	Low	computer-generated random list
Allocation concealment	“All patients meeting eligibility criteria were numbered from 1 to 134 according to the recruitment sequence. Random assignment was accomplished by an independent research nurse” the allocation sequence was masked from the researcher (LC), who was responsible for enrolling and assessing participants named in sequentially numbered envelopes (1 to 134)”	Low	We judged Low risk of bias giving random assignment was accomplished by an independent nurse.
Blinding of self-report outcomes	“No patient reported any adverse effect such as fever or acute onset of periodontal infection, during the study”	High	There was no information about blinding. The control group was untreated so the subjects were not blind.
Blinding of subjective outcomes	“ the allocation sequence was masked from the researcher (LC), who was responsible for enrolling and assessing participants named in sequentially numbered envelopes (1 to 134)”	Unclear	The control group was untreated so dentist who gave the treatment cannot be blinded. Even if investigator who was doing the assessment was blinded (no details about blinding), we don’t know whether the investigator was a different dentist as the one who carried out the treatment.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced.
Incomplete outcome--efficacy	“Of 134 patients, eight withdrew and were excluded from statistical analysis.” (3, 2 and 3 in groups 1,2 and 3) “Missing values were imputed using the last observation carried forward method”	Low	Total lost to follow up was less than 20% and the numbers were balanced among groups.
Incomplete outcome--safety	Reason for WD: 1.Control: broke arm (1) Moved (1) Refusal of blood test (1) 2.SRP + OHI + Subgingival MT: Moved (2) Too busy (1) 3.RP + OHI + Supragingival MT: Broke leg (1) Moved (1)	Low	Reasons for withdrawal were well described.
Selective reporting	“Assessment of periodontal conditions... gingival recession (GR)...” “No patient reported any adverse effect, such as fever or acute onset of periodontal infection.”	High	GR was not reported as was mentioned in the methods section. Reporting of adverse events was a kind of vague. It is unclear as to which possible events were assessed other than fever or infection.
Lin 2012	Quote	Judge	comments
Sequence generation	“Random allocations were carried out using random numbers generated by the statistical software package Stata 9.0 (StataCorp, College	Low	Sequence was computer generated

Station, TX, USA)."			
Allocation concealment	"The allocation sequence was concealed from the periodontist (SJL) who was responsible for treating patients and collecting clinical and laboratory data."	Unclear	This was actually describing blinding. There was no information about concealment.
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes.
Blinding of subjective outcomes	"This was a single-blind, parallel-group study. The allocation sequence was concealed from the periodontist (SJL) who was responsible for treating patients and collecting clinical and laboratory data."	High	There were no details about how blinding were carried out. There was no mention of a placebo gel so it does not look as if the patients were blinded. We are not sure how they would have blinded the treating periodontist as he was the one who would have administered the gel.
Blinding of Objective outcomes	NR	NA	There were no available objective outcomes.
Incomplete outcome--efficacy	NR	Unclear	No information about number of lost to follow up and method they used for handling missing data
Incomplete outcome--safety	NR	NA	There was no safety outcome reported in the article.
Selective reporting	NR	High	The data for HbA1c and CRP was poorly reported and therefore unusable in our analysis. There was no information about safety outcomes and lost to follow up.
Koromantzios 2011 (Koromantzios 2012)	Quote	Judge	comments
Sequence generation	"Participants were randomized using a computer program into two groups (30 patients each),"	Low	Sequence was computer generated.
Allocation concealment	"The randomization sequence was generated by one author (P. K.) before patient recruitment. Numbers from 1 to 60 were assigned to patients according to their recruitment date"	Unclear	Not enough detail to judge. e.g. how people in charge of allocation were blinded
Blinding of self-report outcomes	NR	NA	No patient self-reported outcomes
Blinding of subjective outcomes	"Containers (numbered 1–60, four for each visit of each patient) were designated to maintain examiner blinding." "Patients were examined dentally through the course of the study by the same examiner (X. D.) blinded to the allocated group." "Periodontal treatment was administered by the same trained periodontist (P. K.)."	Low	The examiner was blinded and the method of blinding was described. The treatment and assessment were carried out by 2 different dentists.
Blinding of Objective outcomes	"Containers (numbered 1–60, four for each visit of each patient) were designated to maintain examiner blinding."	Low	Blinding was well described and objective outcomes were unlikely to be influenced.
Incomplete outcome--efficacy	"All 60 patients were included in the statistical analysis performed. The seven patients that were lost to follow-up after the 1 month recall visit, were analyzed under the intention-to-treat principle, carrying their last observation forward (Lachin 2000)." Withdrawals: CG: 3/30=10% IG: 4/30=13%	Low	Lost to follow up was less than 20% and balanced between groups. Even though the handling of missing data was not optimal (LOCF), the numbers lost were small enough so as not to bias the results.
Incomplete outcome--	"Out of the seven patients that increased their insulin dosages, five (three in the IG and two in	Unclear	The reasons of withdraws were still unclear.

safety	the CG) were patients that were lost to follow-up"		
Selective reporting	NR	High	No safety outcome was reported. Clinical data at 1, 3, 6 months visit were not reported (only reported change from baseline to 6 months). Secondary outcomes were reported but they did not report PPD and CAL. (They did report PPD and CAL but they reported stratified data so that the data was not usable for our analysis).
Pradeep 2013	Quote	Judge	comments
Sequence generation	"a computer- generated random table"	Low	Sequence was computer generated.
Allocation concealment	"The randomization process was made externally by the statistical unit using a computer-generated random table, and investigators were not involved in the randomization process nor were they aware of the assigned group in all outcomes of valuations."	Low	Central randomization
Blinding of self-report outcomes	"Participants were masked for allocation into the SMV or placebo group." "All participants tolerated the drug well without any complications or adverse reactions to the drug."	Unclear	Placebo gel was used in control group for blinding of patients but there is no description of the placebo gel (i.e. same tasted and smell etc.).
Blinding of subjective outcomes	"...investigators were neither involved in the randomization process nor were they aware of the assigned group in all outcome evaluations" "All pretreatment and post-treatment clinical parameters we recorded by an examiner who was masked to the type of treatment received by the participants, whereas another clinician provided treatment to both groups."	Low	Randomization process was conducted separately. Clinical examiner who assessed periodontal parameters was different as the clinician who provided the treatments.
Blinding of Objective outcomes	"...investigators were neither involved in the randomization process nor were they aware of the assigned group in all outcome evaluations"	Low	Blinding was well described and objective outcomes were unlikely to be influenced.
Incomplete outcome-- efficacy	"35 of 38 participants (multiple sites per participant) completed the study." (Placebo 18/19, Simvastatin 17/19)	Low	Total lost to follow up was less than 20% and the number was balanced between groups.
Incomplete outcome-- safety	"35 of 38 participants (multiple sites per participant) completed the study." (Placebo 18/19, Simvastatin 17/19) "All participants tolerated the drug well without any complications or adverse reactions to the drug."	Unclear	The reasons for lost to follow up were unclear. Even though they said that there were no adverse reactions we don't know for sure if the lost to follow were related to treatment tolerance.
Selective reporting	NR	Low	Protocol is not available for assessment. However, outcomes specified in the methods section were well reported in the results.
Santos 2013	Quote	Judge	comments
Sequence generation	"The study coordinator (PMD) used a computer-generated table to randomly allocate the subjects to test (FMD: FMSRP plus CHX) or control group (FMSRP plus placebo solutions)"	Low	computer-generated table
Allocation concealment	"Identical plastic bottles containing the placebo or CHX gels and rinses were sent to the study coordinator, who marked the code number of each subject on each bottle, according to the therapy assigned."	Unclear	Insufficient information about how they blinded the coordinator.
Blinding of self-report outcomes	"The coded bottles were given to the operator (JAL), who at no time during the study identified the contents of the bottle or subject assignment to therapies. In addition, the biostatistician (MF) and volunteers were also blinded to treatment assignment." "All subjects also answered a questionnaire	Low	Patients in both groups got SRP and medicine contained with identical plastic bottles. Placebo had the same color/smell.

	(administered by a study assistant) about any self-perceived side-effects of the mouthwashes on the 60th day." The placebo solutions were mainly composed of aspartame, zinc acetate dehydrates, alcohol, colourant, flavouring, acesulfame and purified water. The test solutions were composed of the same components of placebo solutions plus chlorhexidine digluconate."		
Blinding of subjective outcomes	"The examiner was unaware of the treatment allocation of the subjects." "The coded bottles were given to the operator (JAL), who at no time during the study identified the contents of the bottle or subject assignment to therapies. However, since continuing CHX rinsing could stain the tooth/tongue surfaces, the examiner could deduce the subjects that were receiving CHX or placebo solutions. For this reason, this study was not considered double-blinded."	High	Since examiner could deduce the subjects that were receiving CHX or placebo solutions, we judged High of blinding.
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be affected by lacking of blinding.
Incomplete outcome--efficacy	"...one from the control group did not return for the 3-month follow- up visit and was not included into the statistical analysis....Two subjects per group did not return for the 12-month visit. Therefore, intention-to-treat analyses were performed in these four subjects (their 6-month data were carried forward)."	Low	Total lost to follow up was less than 20%.(Even though the method of handling missing data (LOCF) was not optimal, this would be unlikely to effect the results given the small number of lost to follow.)
Incomplete outcome--safety	"Seventeen subjects from the FMD group and 12 from control group reported one or two adverse events to the rinses including changes in taste perception, dry mouth and staining." "..."...one from the control group did not return for the 3-month follow- up visit and was not included into the statistical analysis....Two subjects per group did not return for the 12-month visit. "	Unclear	Reasons for lost to follow up were unclear.
Selective reporting	"The subjects from both groups reported no adverse effects such as fever and indisposition after treatment." Seventeen subjects from the FMD group and 12 from control group reported one or two adverse events to the rinses including changes in taste perception, dry mouth and staining."	High	Reporting of adverse effect was vague and the data was not useable for analysis. Patients were given a questionnaire regarding adverse events however the reporting of those events was incomplete and we are not sure of all the AEs that were assessed.
Pradeep 2012	Quote	Judge	comments
Sequence generation	"Patients were randomly by a computer-generated system assigned..."	Low	Sequence was computer generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"Participants were masked for allocation into the ALN or placebo group" "All participants tolerated the drug well without any complications or adverse reactions to the drug."	Unclear	Insufficient information of blinding i.e. no description provided regarding the placebo gel.
Blinding of subjective outcomes	"All pre- and post-treatment clinical parameters were recorded by an examiner (ARP) who was masked to the treatment received, whereas another clinician (AS) provided treatment to both groups"	Low	They had a different person assessing from the one who provided the treatment.
Blinding of Objective outcomes	NR	NA	There was no objective outcomes reported.
Incomplete	"One in each of the ALN and placebo groups	Low	Total lost to follow up was less than 20% and the

outcome--efficacy	failed to follow up"		number was balance between groups.
Incomplete outcome--safety	"One in each of the ALN and placebo groups failed to follow up" "All participants tolerated the drug well without any complications or adverse reactions to the drug."	Unclear	The reasons for lost to follow up were unclear.
Selective reporting	NR	Low	No protocol available but all pre-pacified outcomes were reported.
Gilowski 2012	Quote	Judge	comments
Sequence generation	"Following SRP, patients were randomly (block randomization method) assigned to one of the study group."	Unclear	We don't know how they generated the random number.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"All study personnel and participants were blinded to the treatment assignment for the duration of the study." placebo group used indistinguishable placebo bid	Low	Indistinguishable placebo was used for blinding of patients.
Blinding of subjective outcomes	"Only the study statisticians and the data monitoring committee saw un-blinded data, but none had any contact with study participants." "All study personnel and participants were blinded to the treatment assignment for the duration of the study." placebo group used indistinguishable placebo bid	Low	Placebo was indistinguishable and the personnel were blinded.
Blinding of Objective outcomes	"Only the study statisticians and the data monitoring committee saw un-blinded data, but none had any contact with study participants."	Low	Placebo was indistinguishable and the personnel were blinded. Furthermore, objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	NR	Unclear	They did not report number of lost to follow up. They did talk about the statistics use in the analysis but they didn't report whether or not the analysis was ITT or their plan for handling missing data.
Incomplete outcome--safety	NR	Unclear	They did not report number and reason of lost to follow up.
Selective reporting	NR	High	They only reported median, lower and upper quartile. Mean, SD or SE were not reported. (IN addition they did not report the values for CAD and PD. Results were presented in graph format only.) They also did not report the number of withdraws and number of subjects used for analysis.
Mendonc 2012	Quote	Judge	comments
Sequence generation	"The computer-generated table randomly distributed the right quadrant in one of the two therapeutic groups."	Low	Sequence was computer generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"The subjects did not report adverse effects such as fever and indisposition after treatment. Six subjects reported one or two adverse events to the medication including diarrhea, vomiting, headache, metallic taste or irritability. All subjects informed full adherence to the medications."	High	This is a split mouth RCT. One quadrant received Surgical periodontal therapy and the other received Non-surgical periodontal therapy. Patients could deduce whether the quadrants received SD or NSD. We don't consider patients are blinded.
Blinding of subjective outcomes	"This study was not considered blind as the examiner could deduce whether the quadrants received SD or NSD, as surgery may cause visible sequels in the periodontal tissues."	High	Examiner could deduce whether the quadrants received SD or NSD.

Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"There were no subject or site dropouts during the study (Fig. 1)."	Low	There were no withdrawals.
Incomplete outcome--safety	Same as above	Low	There were no withdrawals.
Selective reporting	NR	Low	Though protocol is not available, they have reported the outcomes that mentioned in the methods section. Safety outcomes as well as withdrawals were also reported.
Moeintaghavi 2012	Quote	Judge	comments
Sequence generation	"Patients were randomly divided into treatment and non-treatment (control) groups by the study research assistant (KK) using a computer generated random numbers table."	Low	Sequence was computer generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes.
Blinding of subjective outcomes	"All subjects underwent a comprehensive clinical examination by a single examiner (AMT) who was an expert periodontist and blinded to the subjects' group assignment."	Unclear	Insufficient information regarding method of blinding.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"There were no dropouts in both groups so we used per protocol analysis."	Low	No withdrawals
Incomplete outcome--safety	"There were no dropouts in both groups so we used per protocol analysis."	Low	No withdrawals
Selective reporting	NR	High	They did not report safety outcomes.
Santos 2012	Quote	Judge	comments
Sequence generation	"...were randomly assigned by the toss of a coin by the same assessor (PMD)...."	Low	Tossing a coin is considered as random.
Allocation concealment	"...were randomly assigned by the toss of a coin by the same assessor (PMD)...."	Unclear	We don't know if the assessor knew which group the subjects were being assigned to by the coin toss and if any caution was taken to prevent assessor switching patient's group.
Blinding of self-report outcomes	"No subjects reported any adverse effects, such as fever or indisposition during the study." "masked randomized and controlled clinical trial"	High	No information about how patients were blinded and based on the nature of invention, patients were unlikely to be blinded. Study described as masked but since the procedure was not amenable to placebo treatment, the masking would not have included the patients.
Blinding of subjective outcomes	"The examiner was unaware of the treatment assignment and the metabolic status of the subjects." "The biostatistician was unaware of the treatment assignment or the metabolic status of the subjects." "masked randomized and controlled clinical trial"	Unclear	Insufficient information regarding the method of blinding
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--	"No subject dropped out of the study"	Low	No withdrawals

efficacy			
Incomplete outcome--safety	"No subject dropped out of the study"	Low	No withdrawals
Selective reporting	NR	Low	Even though there is no protocol available, they reported the outcomes specified in the methods section and we had adequate data for our analysis. They also reported adverse effect and number of withdrawals.
Engelbreton 2011	Quote	Judge	comments
Sequence generation	"45 type 2 diabetes patients were randomly assigned by a computer-generated table to receive sub-antimicrobial-dose doxycycline (20 mg bid for three months) plus scaling and root planning (n = 15), or antimicrobial-dose doxycycline (100 mg each day for 14 days) plus scaling and root planning (n = 15), or placebo for three months plus scaling and root planning (n = 15)."	Low	Sequence was computer generated.
Allocation concealment	"Vials containing the study medications were labeled with a unique code"	Unclear	We don't know whether the code on the vials was open code or not.
Blinding of self-report outcomes	"Placebo tablets were kindly provided by ... Antimicrobial dose doxycycline tablets were obtained ...which were visually indistinguishable from the SDD or placebo tablets. All study patients were assigned to receive the same total number of pills each day for the duration of the study. Each subject received two vials at the baseline visit with instructions to take one tablet from one vial in the morning, and one tablet from the other vial each evening for the first two weeks. Hence, subjects in the antimicrobial dose group received one vial containing 14 tablets of 100 mg doxycycline and one vial containing 14 identical placebo tablets, while subjects in the sub antimicrobial- dose doxycycline group received 14 tablets of 20 mg doxycycline in each vial, and placebo subjects received 14 tablets of placebo in each vial." "Adverse events were monitored and recorded throughout the study." "There were no serious adverse events reported during the study."	Low	Patients were blinded using identical placebo.
Blinding of subjective outcomes	NR	NA	No subjective outcome reported
Blinding of Objective outcomes	"double masked"	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"The data were analyzed on an intent-to-treat basis. The last recorded HbA1c values of subjects who dropped from the study or who were lost to follow up were carried forward" "Of the 10 subjects who were lost to follow up, 3 were from the placebo group, 6 from the SDD group, and 1 from the ADD group" "the attrition rate in this study was high, at 22% with a high number of those occurring in the SDD group, resulting in only 9 completed subjects in this group."	High	Total lost to follow up was more than 20% and no proper imputation was used.
Incomplete outcome--	"There were no serious adverse events reported during the study."	Unclear	The reasons for lost to follow up were unclear.

safety	"Of the 10 subjects who were lost to follow up, 3 were from the placebo group, 6 from the SDD group, and 1 from the ADD group."		
Selective reporting	NR	Unclear	No protocol is available. They stated that the clinical outcomes would be reported elsewhere but we cannot find it.
Khader 2010	Quote	Judge	comments
Sequence generation	"A total of 58 patients were randomized consecutively to one of the two groups: treatment group and control group"	Unclear	We don't know how sequence was generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes that we can use. (They did give a questionnaire for self-report but not any outcomes we were interested in and they didn't report on any of them.)
Blinding of subjective outcomes	NR	NA	There were no clinical outcomes reported.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"Eight patients (three patients in the treatment group and five patients in the control group) were lost to follow-up or reported use of antibiotics, leaving 50 patients to be included in the analysis." Control group: 5/29=17% Treatment group: 3/29=10%	Low	Per-protocol analysis was used but lost to follow up was less than 20%.
Incomplete outcome--safety	NR	NA	There were no safety outcomes
Selective reporting	NR	High	No safety outcomes were reported.
Deo 2010	Quote	Judge	comments
Sequence generation	"Selected patients underwent scaling and root planning and then were "randomly allocated to either a test or control group."	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"No patient showed adverse reaction to SDD therapy" "Patients in the control group received a placebo capsule BID."	Unclear	Placebo was not sufficiently described.
Blinding of subjective outcomes	NR	Unclear	No information about blinding
Blinding of Objective outcomes	NR	NA	No objective outcomes were reported.
Incomplete outcome--efficacy	"None of the selected patients dropped out before the termination of the study."	Low	No withdrawals
Incomplete outcome--safety	"None of the selected patients dropped out before the termination of the study."	Low	No withdrawals
Selective reporting	NR	High	They did not report number of patients randomized in each group. PI and PBI were not reported as mentioned in the methods section.
Mubarak 2010	Quote	Judge	comments
Sequence generation	"This study is a double-blinded, randomized, placebo-controlled, 12-month multi-center trial." "The subjects at each hospital were allocated	High	"Sequentially allocating" is not an acceptable way of randomization.

	numbers which were used to randomize the different groups. This was achieved by distributing the subject number among the four test groups by sequentially allocating them to one of four alphabetical codes relating to a test group (i.e., A for group 1, B for group 2, C for group 3, and D for group 4).” “		
Allocation concealment	Same as above	High	Patients and most importantly investigators may foresee allocation.
Blinding of self-report outcomes	“The examiners as well as the dental hygienist in the different hospital were all blinded to the assigned treatment. Subjects were also blinded to the prescribed medication (doxycycline hyclate, 20 mg or placebo).”	NA	No patient self-reported outcomes
Blinding of subjective outcomes	Same as above	Unclear	Insufficient information about method of blinding (i.e. identical placebo)
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	“Twenty-three subjects did not continue at several intervals during the 12 months of the study, for reasons that violated the inclusion criteria – i.e., taking an antibiotic during the study period, extraction of tooth/teeth, minor or major surgical intervention during the study period, or due to loss of contact information. It should be mentioned here that those who failed to show up at any time point after the baseline visit or failed to show at the last visit (12 months) were also completely excluded from the study. A total of 346 subjects continued until the end of the study.”	Unclear	They did not report numbers of withdrawals by group. (Note: There was only a 6% withdrawal rate but it looks as if there might have been a differential withdrawal rate between groups judging by the final Ns but this is speculative as we don't know the original randomized Ns.)
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	They did not report safety outcomes. In addition the data for HbA1c was not completely reported in the text and some of the time points had to be extracted from the graph.
Al-Zahrani 2009	Quote	Judge	comments
Sequence generation	'... A simple randomization approach using computer-generated random numbers...’	Low	Sequence was computer generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	“None of the patients reported any complications associated with the use of PDT therapy, such as burning sensations, discomfort or pain.” “single masked”	High	No information about how patients were blinded. It does not appear as if the patients were blinded as no placebo treatments were used. The “single masked” description appears to apply to the assessor.
Blinding of subjective outcomes	“The pre- and post-treatment examinations were recorded by the same examiner who was masked to the treatment assignment.” “To ensure masking of the examiners, the investigator who conducted the examination for a patient was not aware or involved in the patients’ treatment.”	Unclear	Although the investigators appeared to have been blinded the patients were not and we don't know if any precautions were taken to prevent a break in the blinding.
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	“Two patients were lost to follow-up; one traveled outside the country, and the other one refused to return for follow-up. Thus, a total of 43 subjects completed the study”	Low	Total withdrawals were less than 20%. Numbers of withdrawals were balanced between groups.

Incomplete outcome--safety	Same as above	Unclear	The reasons for the other withdrawals were unclear.
Selective reporting	NR	High	GR was not reported as mentioned in methods section.
Santos 2009	Quote	Judge	comments
Sequence generation	"...were randomly assigned by the toss of a coin by the same assessor (PMD)...."	Low	Tossing a coin is considered as random.
Allocation concealment	"...were randomly assigned by the toss of a coin by the same assessor (PMD)...."	Unclear	We don't know if the assessor knew which group the subjects were being assigned to by the coin toss and if any caution was taken to prevent assessor switching patient's group.
Blinding of self-report outcomes	"No subjects reported any adverse effects, such as fever or indisposition during the study." "masked randomized and controlled clinical trial"	High	No information about how patients were blinded and based on the nature of invention, patients were unlikely to be blinded. Study described as masked but since the procedure was not amenable to placebo treatment, the masking would not have included the patients.
Blinding of subjective outcomes	"The examiner was unaware of the treatment assignment and the metabolic status of the subjects." " "The biostatistician was unaware of the treatment assignment or the metabolic status of the subjects." "masked randomized and controlled clinical trial"	Unclear	Insufficient information regarding the method of blinding
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"No subject dropped out of the study"	Low	No withdrawals
Incomplete outcome--safety	"No subject dropped out of the study"	Low	No withdrawals
Selective reporting	NR	Low	Even though there is no protocol available, they reported the outcomes specified in the methods section and we had adequate data for our analysis. They also reported adverse effect and number of withdrawals.
Katagiri 2008	Quote	Judge	comments
Sequence generation	"Forty-nine subjects compatible with the medical and dental criteria were randomly allocated to either the periodontal treatment (intervention) or non-periodontal treatment (control) groups by the envelope method."	Unclear	Insufficient information to judge
Allocation concealment	"Forty-nine subjects compatible with the medical and dental criteria were randomly allocated to either the periodontal treatment (intervention) or non-periodontal treatment (control) groups by the envelope method."	Unclear	Insufficient information about the envelope method
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes. Patients would not have been blinded as the control group was untreated.
Blinding of subjective outcomes	NR	Unclear	There was no description of blinding of assessors.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"Finally, 49 participants fulfilled both medical and dental inclusion criteria." "Forty-nine subjects...were randomly allocated." "The analyzed participants included 32 patients in the intervention group and 17 patients in the	Low	No withdrawals

	control group."		
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	They did not report safety outcomes. Data for HbA1c were only reported in graph format. No numeric values were provided.
O'Connell 2008	Quote	Judge	comments
Sequence generation	"Subjects were randomly assigned."	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no patient self-reported outcomes.
Blinding of subjective outcomes	"The SRP group received placebo instead of doxycycline".	Unclear	Patients received placebo but there was no description of the placebo or the blinding of the assessors.
Blinding of Objective outcomes	"The SRP group received placebo instead of doxycycline".	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"Five of the initial 35 subjects were excluded from the study."	Unclear	Withdrawals were less than 20%, but they did not report the losses by group so we don't know if there were differential between groups.
Incomplete outcome--safety	"Five of the initial 35 subjects were excluded from the study. Two subjects were eliminated because they did not finish the treatment phase, two subjects were eliminated because they had to use an anticoagulant agent, and one subject died."	NA	There were no useable safety outcomes.
Selective reporting	NR	High	They did not adequately report safety outcomes. There were adverse events that we could not use in our analysis as they did not report the group that they occurred in. They did not report the number of withdrawals in each group so that we were unable to use any withdrawal outcome.
Skaleric 2004	Quote	Judge	comments
Sequence generation	"After completion of SRP, patients were randomized by envelope to two groups, test or control."	Unclear	Sequence generation was not described.
Allocation concealment	Same as above	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	Unclear	It looks as if the patients were not blinded as there was no mention of a placebo. The study was described as single blind and in the absence of a placebo. One would think that it was the assessors that were blind possibly through separate treating and assessing dentists - although this is not stated. So unclear as to whether or not the patients were blind. Even if they were there is no description of the method of blinding.
Blinding of subjective outcomes	"The control group received only SRP." "single blind"	Unclear	Assessors may have been blinded to treatment allocation but description was insufficient to make a judgement.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"All twenty patients completed the study and no major adverse events were reported."	Low	No withdrawals
Incomplete outcome--safety	"All twenty patients completed the study and no major adverse events were reported."	Low	No withdrawals

Selective reporting	NR	Low	Although they did not report any adverse events other than “major” and there is no published protocol available, the study is judged Low as all outcomes specified in the methods section were reported and we had adequate data for our analysis.
Lima 2004	Quote	Judge	comments
Sequence generation	“Two sites per patient or a total of 22 periodontal defects from the eleven patients in the maxillary incisor or canine areas were randomly assigned to be treated with thorough scaling and root planning under local anesthesia.”	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There was no patient self-reported outcome.
Blinding of subjective outcomes	“As a double blind study design, the operator and the patients were blind whether a syringe contained the test or control gel.”	Unclear	Method of blinding was not sufficiently described.
Blinding of Objective outcomes	Same as above	NA	No objective outcomes were reported
Incomplete outcome--efficacy	“No experimental site was lost in this study.”	Low	11 patients were randomized and 11 were analyzed. It looks as if all patients completed.
Incomplete outcome--safety	NR	NA	They did not report any adverse event.
Selective reporting	NR	High	They did not report safety outcomes. (Although being a split mouth design, only local adverse events would be applicable.)
Al-Mubarak 2002	Quote	Judge	comments
Sequence generation	“The study was randomized by allowing the subjects to self-select a coded number contained in an envelope from 1 to 52 (26 identifying control group and 26 identifying test group) by an independent examiner.” “They were then randomized to 2 different groups with 26 subjects for each group.”	Unclear	No description of how code was generated.
Allocation concealment	Same as above	Low	Here we judged Low because allocation was carried out by an independent examiner.
Blinding of self-report outcomes	NR	NA	There was no self-reported outcome.
Blinding of subjective outcomes	“The clinicians conducting the study were blinded to the identity of the powered oral irrigator.” “Care was taken that subjects do not disclose their group categories to the clinicians and examiners performing the study.” “Single blind”	Low	The powered oral irrigator was applied by patients themselves therefore patients were not blinded. We judged Low risk of bias because “Care was taken that subjects do not disclose their group categories to the clinicians and examiners performing the study”.
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	“2 patients (1 male and 1 female) from each group dropped out of the study before the last visit.”	Low	Withdrawals were less than 20%.
Incomplete outcome--safety	NR	NA	There was no safety outcomes reported.
Selective reporting	NR	High	They did not report safety outcomes. And no reasons were given for withdrawals.
Rocha 2001	Quote	Judge	comments

Sequence generation	"Treatment and control groups were formed matching pairs of patients by gender and number of years since diabetes diagnosis who were then randomly allocated to treatment or control group."	Unclear	Method of randomizing the pairs was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"Both patients and the examiner were blind to the treatment group."	NA	There were no patient self-reported outcomes.
Blinding of subjective outcomes	"Patients received ALN 10 mg/day. Subjects in the control group received capsules with a trivitamin preparation." "All patients received identical periodontal assessment and treatment." "Scaling and root planning of all patients was carried out by one author (CV)." "All measurements were done by the same investigator (CV)." "After allocation to treatment or control groups, patients were followed in a double-blind manner."	Unclear	Placebo was not described as identical. Method of blinding was not described.
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	NR	Unclear	They did not report number of withdraws and methods they used for analyzing.
Incomplete outcome--safety	NR	NA	There was no safety outcomes reported.
Selective reporting	NR	High	They did not report safety outcomes as well as number of withdraws and methods for analysis.
Kaur 2015	Quote	Judge	comments
Sequence generation	"The remaining 100 patients were stratified by HbA1c level into those with good (G group; n = 48) and poor (P group; n = 52) glycemic control. An HbA1c of <7% was used as the cutoff for this classification (34). These patients were then further randomly allocated to either the treatment group (T group; those receiving nonsurgical periodontal therapy in the form of scaling and root planning [SRP]) or the no-treatment group (NT group) (n = 50 each). Computer software was used to avoid a disparity in HbA1c distribution between the two groups."	Low	Sequence was computer generated.
Allocation concealment	"A number from 1-100 was assigned to patients according to their recruitment date."	Unclear	Allocation concealment was not described.
Blinding of self-report outcomes	NA	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	"A single examiner (S.C.N.), blinded to the group allocation, was responsible for recording periodontal parameters throughout the study." "Periodontal treatment of patients in treatment groups was carried out by a different trained examiner (P.K.K.), to avoid any bias in the evaluations."	Low	There were separate clinicians performing treatment and outcome assessment.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"All 125 patients were included in the statistical analysis. The nine patients who withdrew after 3 months (five from T group and four from NT group) were included in intention-to treat analysis by carrying their last observation"	Low	Although LOCF was used and is not the optimal method for handling missing data, the withdrawal rate was low. We can still judge it as Low.

	forward.”		
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	There were no safety outcomes.
Rodrigues 2003	Quote	Judge	comments
Sequence generation	“The subjects were randomly distributed into two groups...”	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	“24 hours prior to the first session group 1 received systemic amoxicillin clavulanic acid 874m twice daily for 2 weeks. The experienced investigator (DCR) conducted all examinations and treatments and antibiotic compliance was monitored during recall visits.”	High	Study was not placebo controlled, there was no mention of blinding and the same dentist carried out the treatments as well as the assessments.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	NR	Unclear	There was no reporting of withdrawals or completion rate.
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	There was no information about number of withdrawals, or any reporting of adverse events (AE).
Fu 2006	Quote	Judge	comments
Sequence generation	“They were randomly divided into two groups...”	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	NR	Unclear	Patients were not blinded and there was no further description.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	NR	Low	46 patients were randomized. 23 patients in each group were used for data analysis. There were no withdrawals.
Incomplete outcome--safety	NR	NA	There was no safety outcomes reported.
Selective reporting	NR	High	They did not report safety outcomes and number of withdrawals.
Singh 2008	Quote	Judge	comments
Sequence generation	“The selected patients were randomly assigned to three groups (groups A, B, and C) comprising 15 patients each...”	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.

Blinding of subjective outcomes	NR	Unclear	Patients were not blinded and there was no further description.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"The study group comprised 45 patients. They were randomly divided into three groups of 15 patients each."	Low	It appears from Table 2 that 15 subjects in each group were analyzed and there were no withdrawals.
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	They did not report number of withdrawals and safety outcomes.
Sun 2011	Quote	Judge	comments
Sequence generation	"All of the T2DM patients were randomly divided into two groups according to whether they underwent periodontal intervention: T2DM-NT group and T2DM-T group."	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	"the study was not blinded"	High	Clinicians were not blinded and outcomes were subjective.
Blinding of Objective outcomes	"the study was not blinded"	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.
Incomplete outcome--efficacy	"A total of 33 patients did not finish the study. The reasons for dropping out included withdrawal due to personal reasons (such as sickness, no available time) (12 patients), later follow-up visit (21 patients, over 3 months). The data of these patients have been excluded from the data at the baseline (Table 1, 2)."	Unclear	The total withdrawal rate was 17.4%. However given that they did not even report their randomized Ns and numbers lost per group, we don't know if there was a differential loss between groups.
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	They did not report how many patients were randomized and lost to follow up in each group. There was no information about safety outcome. This is a particular problem given that some patients withdrew due to "sickness" and we don't know which group they belonged to.
Telgi 2013	Quote	Judge	comments
Sequence generation	'All of the 60 patients were randomly divided into 3 equal groups...'	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"In this study, the examiner and participants were both blinded."	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	Same as above	High	This study has a three-arm parallel design. Method of blinding was not described. Each group got a different protocol and there was no mention of any placebo. Furthermore, long term use of CHX rinse could stain the tooth or tongue surfaces, examiner may deduce whether patients were in control group or not.
Blinding of Objective outcomes	Same as above	Low	Objective outcomes were unlikely to be influenced by lacking of blinding.

Incomplete outcome--efficacy	"All of the 60 participants completed the study."	Low	No withdrawals
Incomplete outcome--safety	Same as above	Low	Withdrawals due to adverse effect equals to zero.
Selective reporting	NR	High	There were no safety outcomes. (Withdrawals due to AE could be ascertained only because there were no withdrawals.)
Gay 2014	Quote	Judge	comments
Sequence generation	"Permuted blocks randomization with varying block sizes using Stata 11 was performed by a statistician (DT) to generate allocation sequences."	Low	Sequence was computer generated.
Allocation concealment	"These sequences were used by the research coordinator (AC) to recruit and blindly randomize 154 participants either to a control (n = 77) or experimental group (n = 77) with a 1:1 allocation ratio."	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	NR	Unclear	There was no mention of blinding anywhere in the study with the exception of HbA1c readings.
Blinding of Objective outcomes	"The personnel who conducted the readings were blinded as to which group the patient belong."	Low	Assessor of objective outcomes was blinded and the outcomes were unlikely to be affected even if lacking of blinding.
Incomplete outcome--efficacy	77 patients were randomized into each group. "The number used for analysis in test and control group is 66 and 60 respectively."	Low	The total lost to follow up was less than 20%.
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	There were no safety outcomes. The number used for analysis in test and control group is 66 and 60 respectively, which was inconsistent with the flow chart.
Priyanka 2015	Quote	Judge	comments
Sequence generation	"32 subjects were randomly (by computer generated system) assigned to each treatment group."	Low	Sequence was computer generated.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	Unclear	No information about how patients were blinded. It appears that the patients were blinded but there is no description of the placebo with which to judge the adequacy of blinding.
Blinding of subjective outcomes	"A single clinician (PN) provided treatment to both groups, and all pre- and post-treatment clinical parameters were recorded by another examiner (ARP) who was masked to the type of treatment received by the subjects."	Low	The study included a separate examiner and that person was described as blinded.
Blinding of Objective outcomes	NR	NA	There were no objective outcomes reported.
Incomplete outcome--efficacy	"Fifty-seven of 64 subjects completed the study. Seven subjects did not follow up after the baseline examination. Fifty-seven treatment sites (one site/subject) were evaluated for clinical parameters at baseline." Withdrawals: Placebo 3/32=9% Treatment 4/32=13%	Low	Total withdrawals were less than 20% and balanced between groups.

Incomplete outcome--safety	"Fifty-seven of 64 subjects completed the study. Seven subjects did not follow up after the baseline examination."	Unclear	The reasons of withdraws were unclear. We don't know the reasons for withdrawal so cannot rule out adverse events as the cause.
Selective reporting	NR	Low	No protocol is available. Paper reported the outcomes that have been specified in the methods section. Adverse events were reported (although more detail could have been provided).
Artese 2015	Quote	Judge	comments
Sequence generation	"This study comprised 24 individuals randomly assigned by a computer random number generator (Excel), and allocated by sequentially numbered sealed opaque envelopes."	Low	Sequence was computer generated.
Allocation concealment	Same as above	Low	Sequentially numbered opaque envelopes
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	"Periodontal therapy was carried out by an experienced periodontist (G.H.G.)" "Clinical examinations were performed by two blinded and calibrated examiners (H.P.C.A. and A.M.F.)"	Low	Although periodontal treatments were different between groups, the outcome assessors were blind and did not perform the treatment.
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be affected by lacking of blinding.
Incomplete outcome--efficacy	There is no lost to follow up.	Low	No withdrawals
Incomplete outcome--safety	There is no lost to follow up.	Low	Withdrawals due to adverse effect equals to zero.
Selective reporting	NR	High	They did not report safety outcomes. (Zero withdrawals due to AE were available through complete follow up.)
Gaikwad 2013	Quote	Judge	comments
Sequence generation	"The selected subjects were randomly assigned to two groups."	Unclear	Sequence generation was not described.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes. (However patients were not blind as a placebo was not used.)
Blinding of subjective outcomes	NR	Unclear	Insufficient information to judge
Blinding of Objective outcomes	NR	Low	Objective outcomes were unlikely to be affected by lacking of blinding.
Incomplete outcome--efficacy	"A total of 50 subjects (34 males and 16 females) were included in the study. Only 42 subjects (31 males and 11 females) completed the study in adherence to the prescribed protocol."	Unclear	Although the total withdrawal rate was less than 20%, they didn't even tell us which group the subjects withdrew from.
Incomplete outcome--safety	NR	NA	There was no safety outcomes reported.
Selective reporting	NR	High	Safety was only reported for the doxycycline group. Withdrawals were not reported by group.
Elwakeel 2015	Quote	Judge	comments
Sequence generation	"Subjects were randomly assigned by the study coordinator (H.S.), using a coin toss into two groups (20 patients each) in a parallel, double-masked design."	Low	Coin toss is considered as random.

Allocation concealment	"Either placebo or x3 PUFAs + aspirin capsules were dispensed by the study coordinator who was the only person who had access to them. Coded medication or placebo packages containing two bottles each (x3 PUFAs + aspirin or placebos) were prepared by the Faculty of Pharmacy of Al-Azhar University. To ensure a proper double-blind study protocol; the bottles were not decoded until the end of follow-up evaluations, and after final statistical analysis was done."	Low	The medication bottles had been coded by the pharmacy.
Blinding of self-report outcomes	"Placebo capsules were carefully matched in appearance and flavor with the active treatment."	NA	There were no self-reported outcomes.
Blinding of subjective outcomes	"Initial periodontal examination, full mouth SRP, clinical measurements, gingival crevicular fluid sampling as well as reinforcement of oral hygiene at baseline and during follow-up evaluations were performed by the same periodontist (M.S.), who remained blinded to treatment allocation." "To ensure a proper double-blind study protocol; the bottles were not decoded until the end of follow-up evaluations."	Low	Given that the bottles were not decoded until after the evaluations we judged this as low risk of bias.
Blinding of Objective outcomes	"Double masked" "To ensure a proper double-blind study protocol; the bottles were not decoded until the end of follow-up evaluations."	Low	Objective outcomes were less likely to be affected by lacking of blinding.
Incomplete outcome--efficacy	67 were randomized and a total number of 27 lost to follow up.	High	Over 20% patients lost to follow up. It looks as if they just excluded them so did not use any method for handling missing data.
Incomplete outcome--safety	NR	NA	There was no safety outcomes reported.
Selective reporting	"At each visit adverse side effects were recorded." "Thirteen subjects in the intervention group reported nausea, abdominal upsets and irritating fish-scented halitosis side effects that were not strong enough to stop the treatment regimen."	High	Safety outcome were incompletely reported. PI was mentioned in the methods section but was not reported.
Pradeep 2015	Quote	Judge	comments
Sequence generation	"Patients were selected based on these criteria (by VG) and coin toss was used to randomly allocate 30 patients to each treatment group"	Low	Coin toss is considered as random.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"Both AV gel and placebo gel were prepared similar in color and consistency so as not to affect the examiners blinding."	Low	Placebo was described as similar in color and consistency.
Blinding of subjective outcomes	"Treatment to both the groups was provided by a single clinician (VG) and all the pre- and post-treatments were recorded by another examiner (ARP), who was masked to the type of treatment received by the patients."	Low	Outcome assessment was performed by a different clinician than the one who provided the treatment. The method of blinding was described.
Blinding of Objective outcomes	NR	NA	There were no objective outcomes.
Incomplete outcome--efficacy	"All 60 patients completed the study."	Low	No withdrawals
Incomplete outcome--safety	"All 60 patients completed the study."	Low	No withdrawals
Selective reporting	NR	Low	No protocol is available. They reported all of the outcomes listed in the methods section and

			seemed to include the important periodontal measures.
Alshehri 2015	Quote	Judge	comments
Sequence generation	"These individuals were randomly divided into two groups with 30 patients per group by picking out a paper marked either 'group 1' or 'group 2' from an opaque box."	Low	"Drawing of lots" is an acceptable form of randomization.
Allocation concealment	Same as above	Low	They used opaque box that made foresee of allocation unlikely.
Blinding of self-report outcomes	NR	NA	There was no self-reported outcome.
Blinding of subjective outcomes	"A single trained and calibrated investigator (MA), who was blinded to the test- and control- groups, performed the baseline and follow-up periodontal examinations."	Unclear	Patients were not blind as there was no placebo treatment and the method of blinding of investigators was not described.
Blinding of Objective outcomes	NR	Low	Objective outcomes were less likely to be affected by lacking of blinding.
Incomplete outcome--efficacy	60 patients were randomized (30 in each group).	Unclear	We don't know number of withdraws, number they used to analyze in each group and the method they used for analysis.
Incomplete outcome--safety	NR	NA	There were no safety outcomes.
Selective reporting	NR	High	There were no safety outcomes and no reporting of withdraws. PPD outcome could not be used as they only reported the percent of patients who had PPD > 4mm. HbA1c was only reported in graph format with ambiguous variance measure.
Agarwal 2012	Quote	Judge	comments
Sequence generation	"... patients were randomly (by computer generated system) assigned to either Group 1 (SRP + Placebo) or Group 2 (SRP + 0.5% AZM)."	Low	Sequence generation was computerized.
Allocation concealment	NR	Unclear	Insufficient information to judge
Blinding of self-report outcomes	"Patients were blinded for allocation into AZM or placebo group"	Unclear	The placebo gel was not described.
Blinding of subjective outcomes	"All pre and post treatment clinical parameters were recorded by an examiner who was masked to the type of treatment received by the patients while another clinician provided treatment to both groups."	Low	The outcome assessor was a different clinician than the treating dentist. Patients were also blinded.
Blinding of Objective outcomes	NR	NA	There were no objective outcomes.
Incomplete outcome--efficacy	"56 patients out of 63 completed the study." Total withdraws: 7/63=11% Placebo group: 2/32=6% Intervention group: 4/31=13%	Low	The total withdraws were less than 20%. Withdraws between groups are not significantly different.
Incomplete outcome--safety	Same as above	Unclear	Reasons of withdraws were unclear.
Selective reporting	NR	Low	No protocol is available. All outcomes specified in the methods section were reported in the results. Adverse events were reported (although lacking in detail).
Ardakani 2014	Quote	Judge	Comments
Sequence generation	Patients were randomly allocated into either intervention or control group	Unclear	Insufficient information to judge
Allocation concealment	NR	Unclear	Insufficient information to judge

Blinding of self-report outcomes	NR	NA	There is no self-reported outcome.
Blinding of subjective outcomes	All of the patients was treated by one person	Unclear	Insufficient information to judge
Blinding of Objective outcomes	All of the patients was treated by one person	Low	Objective outcomes are unlikely to be influenced by lack of blinding.
Incomplete outcome--efficacy	NR	Unclear	They did no mention about withdrawals. It seems they followed all the participants but we are not sure.
Incomplete outcome--safety	NR	NA	There is no safety outcome.
Selective reporting	NR	High	There is no safety outcome.
Zhang 2013	Quote	Judge	comments
Sequence generation	"Assignment to different groups was made using prepared randomization in group A, B, or C. Participants with A and B were assigned to the treatment group and then respectively assigned to the sub-ERP and sub-prophylaxis groups, whereas individuals with C were assigned to the control group." Cards with group identification were prepared and placed in number-coded envelopes as defined by SPSS.	Low	number coded envelopes defined by SPSS
Allocation concealment	Cards with group identification were prepared and placed in number-coded envelopes as defined by SPSS. "The random code was retained until the last patient had completed the entire study."	Unclear	whether the envelopes were allocated by sequence or opaque are unclear
Blinding of self-report outcomes	NR	NA	There were no self-reported outcomes
Blinding of subjective outcomes	"The single blind method was used in this study as the examiner was blind to the intervention for the patients."	Unclear	It looks as if a separated examiner does the outcome assessment but they don't explicitly say this so we judged unclear.
Blinding of Objective outcomes	The examiner was blind to the intervention for the patients.	Low	Blinding of lab data was not described but objective outcomes were likely unaffected by blinding.
Incomplete outcome--efficacy	Total withdrawals: 3/75=4% Treatment: 1/50=2% Control: 2/25=8%	Low	The lost to follow up rate was less than 20% and balanced between groups.
Incomplete outcome--safety	NR	NA	No safety outcome
Selective reporting	NR	High	They did not report safety outcomes and most of the statistics were reported in the form of graph.
Koçak 2016	Quote	Judge	comments
Sequence generation	"The 60 patients with DM2 did not refer to us as one cohort, but referred as two at a time in the time period detailed above. Then, the two patient ID cards with the patient names not visible were presented to the senior author (SSH), who subsequently and 'blindly' assigned each of the two ID cards to one and another unlabeled, patient file boxes, of which one represented the experimental treatment and the other the control treatment. The treatment mode, represented by the two patient file boxes, was only known to the first author (EK)..."	Low	Similar to drawing lots

Allocation concealment	Same as above	Low	SSH “blindly” assigned patients and the treatment mode was only available to EK.
Blinding of self-report outcomes	NR	NA	There were no safety outcomes.
Blinding of subjective outcomes	“The treatment mode, represented by the two patient file boxes, was only known to the first author (EK), who after the random assignment of the two patients at a time, treated these patients according to the experimental or control mode. For the whole study period, the statistician was masked for the treatment modes.”	NA	No available subjective outcomes
Blinding of Objective outcomes	Same as above	Low	They did not mention whether assessors were blinded but the outcome was objective.
Incomplete outcome--efficacy	NR	Low	There was no drop out.
Incomplete outcome--safety	NR	Low	There was no drop out.
Selective reporting	NR	High	No safety outcome reported

APPENDIX 7: COMBINING OF TREATMENTS

SRP + PLACEBO (TABLET/ GEL/ RISEN/ OR WATER IRRIGATION)

ID	Original description	Treatment after combining
Tsalikis 2014	SRP + placebo	SRP
Miranda 2014	SRP + placebo pills	SRP
Hincapié 2014	SRP + placebo tablets (identical with AZM)	SRP
Bajaj 2012	SRP + placebo gel	SRP
Pradeep 2013	SRP + placebo gel	SRP
Santos 2013	SRP + placebo gel and rinse	SRP
Pradeep 2012	SRP + placebo gel	SRP
Gilowski 2012	SRP + placebo bid (indistinguishable)	SRP
Engebretson 2011	SRP + placebo tablet (visually indistinguishable)	SRP
Deo 2010	SRP + placebo capsule	SRP
Mubarak 2010	SRP + placebo tablet	SRP
O'Connell 2008	SRP + placebo	SRP
Martorelli 2004	SRP+ placebo gel	SRP
Rocha 2001	SRP + placebo capsule	SRP
Priyanka 2015	SRP + placebo	SRP
Elwakeel 2015	SRP + placebo pills/capsule	SRP
Pradeep 2015	SRP + placebo gel	SRP
Alshehri 2015	SRP + tap water	SRP
Agarwal 2012	SRP + placebo gel	SRP

ORAL HYGIENE INSTRUCTION

ID	Description in the article	How delivered	Who delivered	Follow up time	Name in the network
Tsalikis 2014	Oral hygiene reinforcement at 3 and 6 months	NR	NR	at 3 and 6 months follow up visits	OHI
Miranda 2014	They were also instructed regarding the brushing technique and received the same brand of toothpaste during the course of the study (Colgate Total , Colgate Palmolive Co., Sao Paulo, SP, Brazil)	brushing technique and received the same brand of toothpaste	NR	NR	OHI

ID	Description in the article	How delivered	Who delivered	Follow up time	Name in the network
Raman 2014	All subjects were instructed in oral hygiene methods using a soft bristled toothbrush, a compact-tuft toothbrush, interdental brushes and dental floss (TePe® oral hygiene education set) utilizing the modified Bass technique. Plaque scores of the subjects in the NSPT group were reviewed at weekly intervals to achieve scores of 20% or below to a maximum of 3 weeks. Subjects were re-motivated and instructed when necessary.	All subjects were instructed in oral hygiene methods using a soft bristled toothbrush, a compact-tuft toothbrush, interdental brushes and dental floss utilizing the modified Bass technique. Test group has intensive OHI: Plaque scores of the subjects in the NSPT group were reviewed at weekly intervals to achieve scores of 20% or below to a maximum of 3 weeks.	NR	Subjects in both groups were re-motivated and instructed when necessary.	Intensive OHI
Al-Nowaiser 2014	Patients were instructed to brush and floss 2 times a day.	Patients were instructed to brush and floss 2 times a day.	NR	NR	OHI
Macedo 2013	Oral hygiene was reviewed twice monthly, followed by prophylaxis for 3 months in both groups.	Oral hygiene was reviewed	NR	twice monthly for 3 months	OHI
Engebretson 2013	The therapist provided oral hygiene instructions at baseline and 3-, 6-month visits and dispensed toothbrush, toothpaste and dental floss.	Oral hygiene instruction; dispense toothbrush, toothpaste and dental floss.	The therapist	at baseline and 3-, 6-month visits	OHI
Llambés 2012	Subjects were instructed on the modified Bass brushing technique and interproximal cleaning.	Subjects were instructed on the modified Bass brushing technique and interproximal cleaning.	NR	NR	OHI
Chen 2012	OHI (no description)	OHI (no description)	NR	NR	OHI
Lin 2012	oral hygiene instruction	oral hygiene instruction (no description)	NR	NR	OHI
Koromantzos 2011	All participants received oral hygiene instructions at baseline and after each visit.	All participants received oral hygiene instructions (no description)	NR	at baseline and after each visit	OHI
Pradeep 2013	Before SRP, each patient was given careful instructions on proper oral hygiene measures.	Before SRP, each patient was given careful instructions on proper oral hygiene measures.	NR	Before treatment of SRP	OHI
Santos 2013	All subjects were instructed to perform a brushing technique using a soft toothbrush, dental floss and interdental toothbrushes, as necessary, and received the same brand of toothpaste during the study. Re-instruction of oral hygiene was performed at 3, 6 and 9 months post-therapies.	All subjects were instructed to perform a brushing technique using a soft toothbrush, dental floss and interdental toothbrushes, as necessary, and received the same brand of toothpaste during the study.	NR	Re-instruction of oral hygiene was performed at 3, 6 and 9 months post-therapies.	OHI

ID	Description in the article	How delivered	Who delivered	Follow up time	Name in the network
Gilowski 2012	Oral hygiene instruction was given to the patients, including tooth brushing and the use of interdental flossing or interdental brushing as appropriate.	Oral hygiene instruction was given to the patients, including tooth brushing and the use of interdental flossing or interdental brushing as appropriate.	NR	NR	OHI
Moeintaghavi 2012	Prior to the first treatment session, patients in both groups received standard oral hygiene instructions.	Patients in both groups received standard oral hygiene instructions.	NR	Prior to the first treatment session	OHI
Santos 2012	The subjects were instructed to use a soft toothbrush, dental floss and interdental toothbrushes, as necessary, and the same brand of toothpaste for the duration of the study.	The subjects were instructed to use a soft toothbrush, dental floss and interdental toothbrushes, as necessary, and the same brand of toothpaste for the duration of the study.	NR	NR	OHI
Koromantzios 2012	All participants received oral hygiene instructions at baseline and each visit.	oral hygiene instructions (no description)	NR	at baseline and each visit	OHI
Khader 2010	Oral hygiene instructions	Oral hygiene instructions (no description)	NR	NR	OHI
Mubarak 2010	Dental hygiene aids were provided for the subjects- i.e. toothbrush and toothpaste at the baseline visit.	Dental hygiene aids were provided for the subjects- i.e. toothbrush and toothpaste	NR	at the baseline visit	OHI
Al-Zahrani 2009	Individualized oral hygiene instruction for each subject was given and followed by SRP.	Individualized oral hygiene instruction for each subject was given.	NR	NR	OHI
Santos 2009	They were instructed to perform a brushing technique using a soft toothbrush, dental floss, and interdental toothbrushes, as necessary. Moreover, all volunteers received the same brand of toothpaste to use during the course of the study.	They were instructed to perform a brushing technique using a soft toothbrush, dental floss, and interdental toothbrushes, as necessary. Moreover, all volunteers received the same brand of toothpaste to use during the course of the study.	NR	NR	OHI
Katagiri 2008	participants received instructions for brushing their teeth, including the use of inter-proximal cleaning aids, such as floss and inter-dental brushes, depending on their individual needs	participants received instructions for brushing their teeth, including the use of inter-proximal cleaning aids, such as floss and inter-dental brushes, depending on their individual needs	NR	NR	OHI
O'Connell 2008	Oral hygiene was reviewed twice monthly, followed by prophylaxis for 3 months.	Oral hygiene was reviewed	NR	twice monthly for 3 months	OHI
Martorelli 2004	oral hygiene instruction	oral hygiene instruction (no description)	NR	NR	OHI

ID	Description in the article	How delivered	Who delivered	Follow up time	Name in the network
Rocha 2001	Patients were taught and encouraged to maintain their personal dental care and plaque control through mechanical brushing and dental floss.	Patients were taught and encouraged to maintain their personal dental care and plaque control through mechanical brushing and dental floss.	NR	NR	OHI
Kaur 2015	oral hygiene instructions were given at baseline and at each visit	oral hygiene instructions (no description)	NR	at baseline and at each visit	OHI
Rodrigues 2003	All patients' revived standard oral hygiene instructions before the first session of SRP. Oral hygiene control and reinstruction were reviewed two times monthly.	standard oral hygiene instructions (no description)	NR	before the first session of SRP; reinstruction were reviewed two times monthly	OHI
Singh 2008	oral hygiene instructions	oral hygiene instructions (no description)	NR	NR	OHI
Sun 2011	oral hygiene	oral hygiene (no description)	NR	NR	OHI
Telgi 2013	Advised to brush twice daily. The performance was reinforced every month through telephone calls to ensure compliance.	advised to brush twice daily	NR	The performance was reinforced every month through telephone calls to ensure compliance.	OHI
Gay 2014	Patient education regarding periodontal disease and its association with diabetes was given along with oral hygiene instructions including the modified Bass technique, use of inter-proximal toothbrushes and dental floss. Oral hygiene was reinforced 4-6 weeks after baseline examination.	Patient education regarding periodontal disease and its association with diabetes was given along with oral hygiene instructions including the modified Bass technique, use of inter-proximal toothbrushes and dental floss.	NR	Oral hygiene was reinforced 4-6 weeks after baseline examination.	OHI
Artese 2015	All individuals were given oral hygiene instructions. Professional instructions on oral hygiene were given to each patient every month.	All individuals were given oral hygiene instructions (no description)	NR	Professional instructions on oral hygiene were given to each patient every month.	OHI
Elwakeel 2015	oral hygiene instruction was given at baseline and follow up visits by periodontitis.	oral hygiene instructions (no description)	periodontitis	at baseline and follow up visits	OHI
Ardakani 2014	oral hygiene instruction	oral hygiene instructions (no description)	NR	NR	OHI
Zhang 2013	oral health instruction	oral health instructions (no description)	NR	NR	OHI
Koçak 2016	All patients' received oral hygiene instructions at the first visit.	oral hygiene instructions (no description)	NR	at first visit	OHI

ANTIBIOTICS

ID	Description in the study	Name in the network
Telgi 2013	0.12% chlorhexidine mouthwash (once daily)	CHX rinse
Mendonca 2012	Chlorhexidine rinses 0.12% BID for 14 days	CHX rinse
Llambés 2012	Chlorhexidine rinses 0.2% (20ml twice a day for 12 weeks)	CHX rinse
Engebretson 2013	chlorhexidine gluconate 0.12% oral rinse (twice a day for 2 weeks)	CHX rinse
Raman 2014	0.12% Chlorhexidine mouth rinse three times a day (15 ml each time for a period of 14 days)	CHX rinse
Rodrigues 2003	amoxicillin/clavulanic acid (875 mg bid for 14 days)	AMX
Mendonca 2012	Amoxicillin (500 mg TID) for 10 days	AMX
Miranda 2014	AMX (500 mg TID for 14 days)	AMX
Mendonca 2012	Metronidazole (400 mg TID)	MTZ
Miranda 2014	MTZ (400 mg TID for 14 days)	MTZ
Al-Zahrani 2009	Doxycycline (200 mg as loading dose for day 1 and 100mg per day for another 13 days)	Doxy
Singh 2008	Doxycycline (200 mg as loading dose, 100 mg/day for 14 days)	Doxy
O'Connell 2008	Doxycycline (100 mg/day for 14 days with an initial dose of 200 mg)	Doxy
Engebretson 2011	doxycycline (100mg each day for 14 days)	Doxy
Llambés 2012	doxycycline 200mg first day and 100mg for 15 days	Doxy
Gaikwad 2013	Doxycycline (100 mg/day for 15 days)	Doxy
Macedo 2013	Doxycycline (200 mg as loading dose and 100 mg for 14 days)	Doxy
Tsalikis 2014	Doxycycline (200 mg as loading dose and 100 mg for 20 days)	Doxy
Al-Nowaiser 2014	Doxycycline (200 mg as loading dose and 100 mg for 14 days)	Doxy
Gilowski 2012	SDD (doxycycline hydrochloride 20 mg bid for 3 months)	SDD
Engebretson 2011	SDD (20 mg doxycycline bid for 3 months)	SDD
Deo 2010	Doxycycline (20mg bid for 6 months)	SDD
Mubarak 2010	Doxycycline 20mg bid for 3/6 months	SDD
Ardakani 2014	tetracycline gel %5	TET gel
Lin 2012	2% minocycline gel (once a week for 4 weeks)	TET gel
Katagiri 2008	10 mg minocycline ointment (topical)	TET (topical)
Skaleric 2004	minocycline microspheres (PPD >= 5mm) at baseline and 3 months	TET (topical)

MAINTENANCE

ID	Description in the study	Name in the network
Miranda 2014	Supportive therapy sessions were performed at 3, 6, and 9 months post-therapies.	Intensive maintenance
Macedo 2013	Prophylaxis twice monthly for 3 months	Intensive maintenance
Engebretson 2013	Three and 6 months following the baseline visit, treatment group participants received scaling and root planning for approximately one hour during a single session	Intensive maintenance
Chen 2012	Subgingival debridement or supragingival prophylaxis at 3-month follow up	Intensive maintenance
Koromantzos 2011	Test group received additional supportive SRP at each visit.	Intensive maintenance
Santos 2013	Supportive therapy sessions were performed at 3, 6 and 9 months post-therapies including professional plaque control with abrasive sodium carbonate air-powder system, subgingival debridement, as necessary, and re-instruction of oral hygiene.	Intensive maintenance
Mendonca 2012	Supragingival plaque control was performed at 3 months after therapies.	Non-intensive maintenance
Santos 2012	Supportive therapy sessions were performed at 3, 6 and 9 months post-therapy and lasted for approximately 60 min each. The supportive therapy included professional plaque control using an abrasive sodium carbonate air-powder system, subgingival debridement (as necessary) and reinstruction of oral hygiene.	Intensive maintenance
Koromantzos 2012	IG received additional supportive SRP at each visit if judged necessary.	Intensive maintenance
Mubarak 2010	The second session of SRP at 6 month	Intensive maintenance
Santos 2009	The supportive therapy, including professional plaque control with an abrasive sodium carbonate air-powder system and reinstruction of oral hygiene was performed at 3 and 6 months post-therapy.	Intensive maintenance
Katagiri 2008	In the intervention group, additional periodontal treatments including instructions for brushing, supra- and sub-gingival debridement without topical administration of antibiotics were performed, if necessary.	Intensive maintenance
O'Connell 2008	Oral hygiene was reviewed twice monthly, followed by prophylaxis for 3 months.	Intensive maintenance
Skaleric 2004	A timed, 20 minute full mouth supragingival cleaning was performed at the 12-week visit in both rest and control groups.	Non-intensive maintenance
Martorelli 2004	at 3,6,9 and 12 months for maintenance	Intensive maintenance
Kaur 2015	additional supportive SRP was done when necessary at each visit	Intensive maintenance
Rodrigues 2003	Oral hygiene control and reinstruction were reviewed two times monthly, followed by prophylaxis.	Intensive maintenance

APPENDIX 8: EVALUATION OF NETWORK CONSISTENCY

One of the key assumptions in the network meta-analysis is that estimates from indirect comparisons are consistent with those from direct comparisons. We evaluated consistency of network with closed loops. To be classified as a “closed loop,” the nodes had to be connected by different trials (i.e. not connected by one multi-arm trial).

To evaluate the consistency of networks, 2 analyses were performed. One was conducted using the standard consistency model (the model used for primary analyses), which assumes data are consistent in the network. The other was conducted using an inconsistency model, which assumes data in the network may not be consistent. Mean deviance of the individual data points derived from the inconsistency model was plotted against mean deviance derived from the consistency model. If the network is consistent, most of the data points will lie along the diagonal line indicating the estimates are similar from both models. If inconsistency is present, data points will deviate off the diagonal line.

FIGURE A8.1 HBA1C: BASE CASE (3 MONTHS)

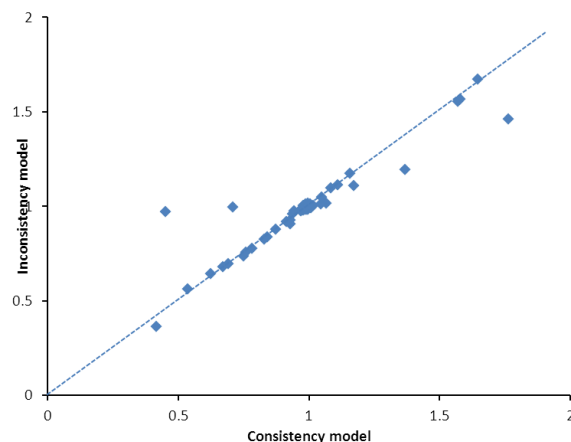


FIGURE A8.2 HBA1C: NO INDUSTRY FUNDING (3 MONTHS)

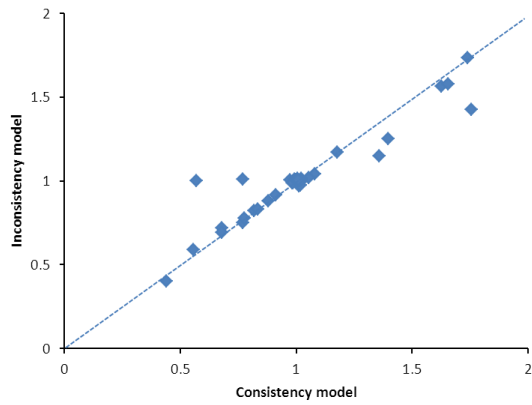


FIGURE A8.3 HBA1C: LOW/UNCLEAR RISK OF BIAS (3 MONTHS)

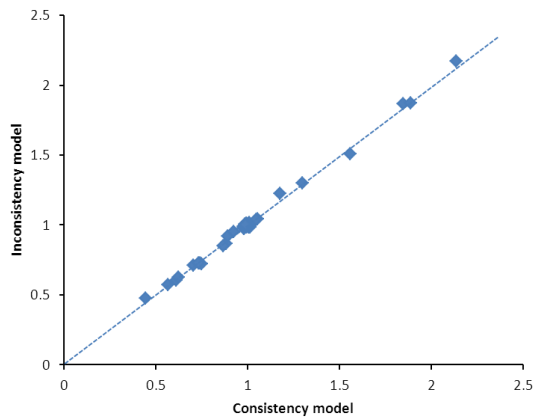


FIGURE A8.4 HBA1C: EXCLUDE LONG TERM USR OF CHX RINSE (3 MONTHS)

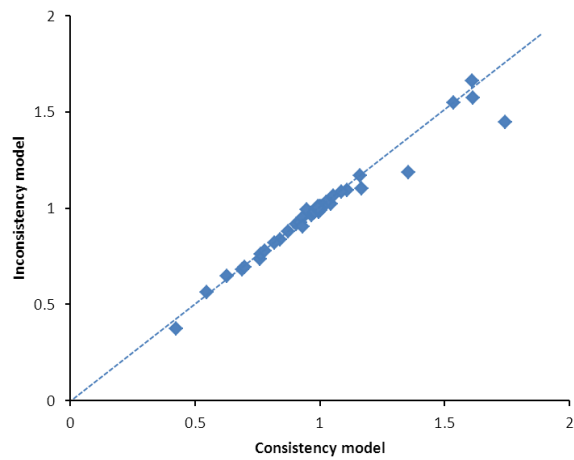


FIGURE A8.5 HBA1C: PARTIAL MOUTH SRP (3 MONTHS)

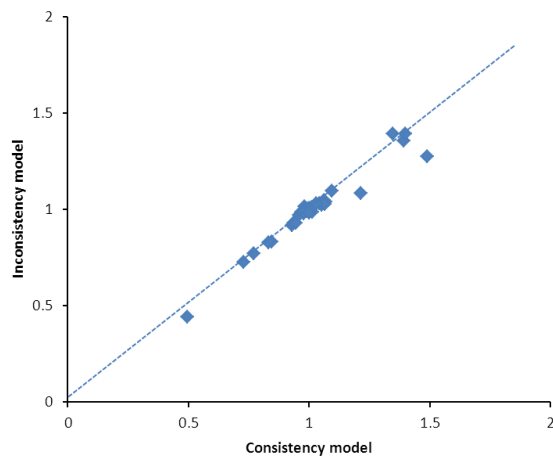


FIGURE A8.6 HBA1C: AGE < 65 YR (3 MONTHS)

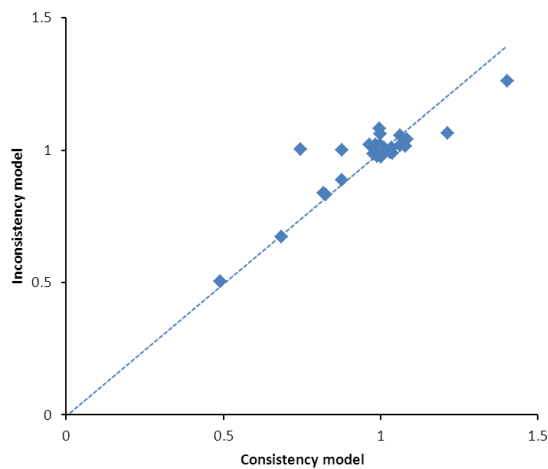


FIGURE A8.7 HBA1C: TRIALS WITH TYPE 2 DIABETIC PATIENTS (3 MONTHS)

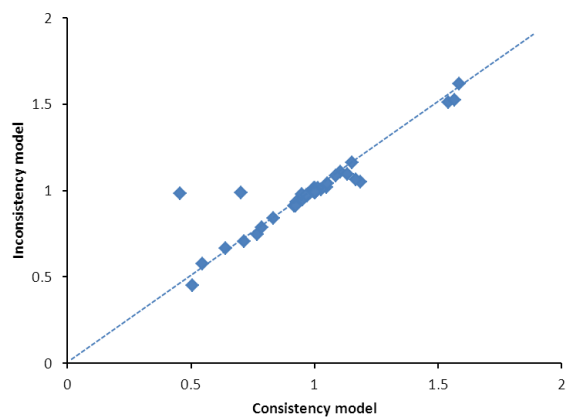


FIGURE A8.8 HBA1C: TRIALS WITH BASELINE PPD <5MM (3 MONTHS)

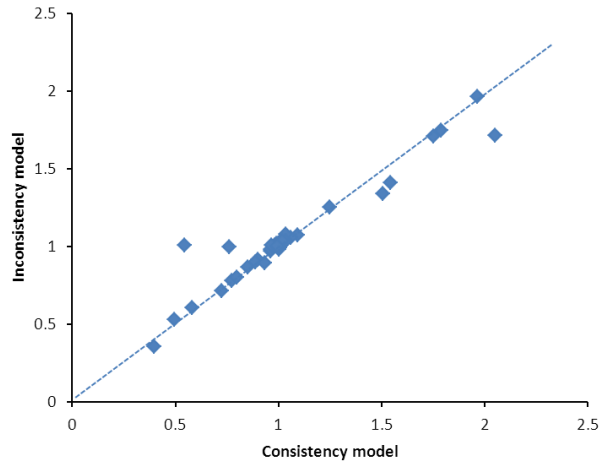


FIGURE A8.9 HBA1C: BASE CASE (END OF STUDY)

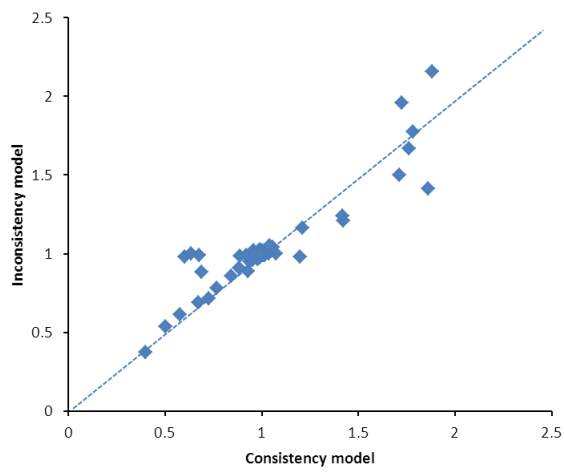


FIGURE A8.10 HBA1C: NO INDUSTRY FUNDING (END OF STUDY)

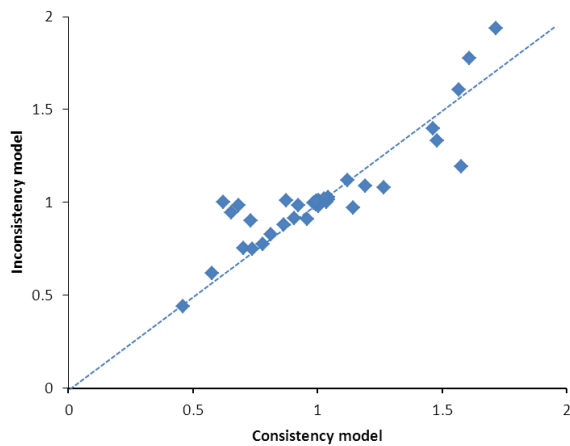


FIGURE A8.11 HBA1C: LOW/UNCLEAR RISK OF BIAS (END OF STUDY)

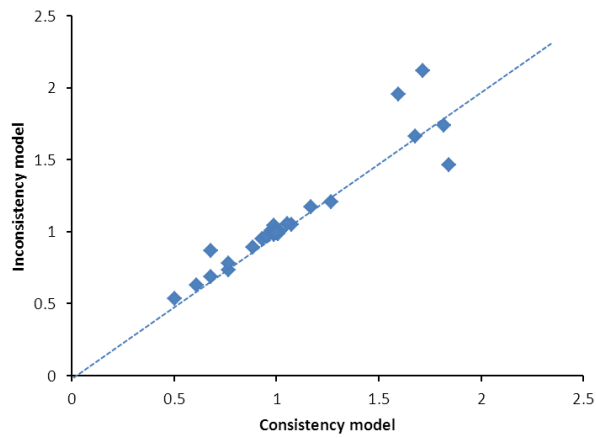


FIGURE A8.12 HBA1C: EXCLUDE LONG TERM USR OF CHX RINSE (END OF STUDY)

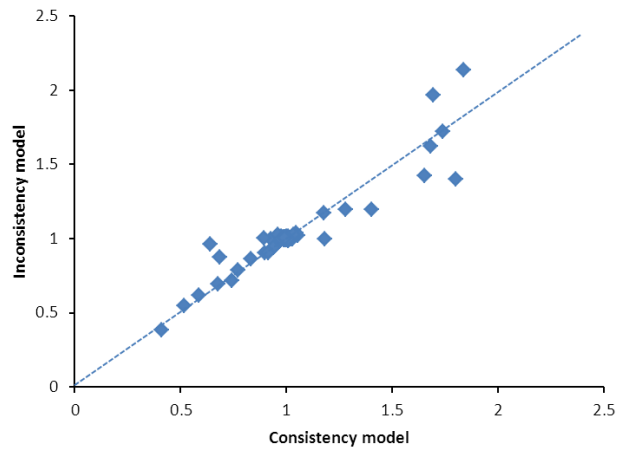


FIGURE A8.13 HBA1C: PARTIAL MOUTH SRP (END OF STUDY)

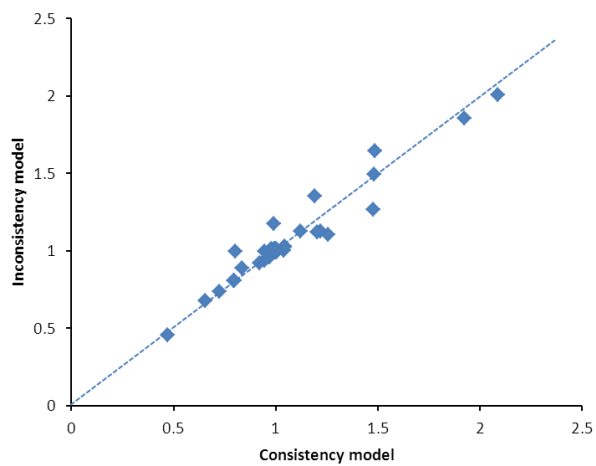


FIGURE A8.14 HBA1C: AGE < 65 YR (END OF STUDY)

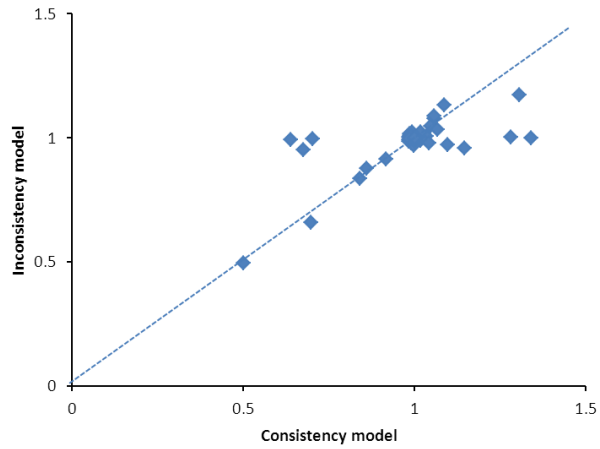


FIGURE A8.15 HBA1C: TRIALS WITH TYPE 2 DIABETIC PATIENTS (END OF STUDY)

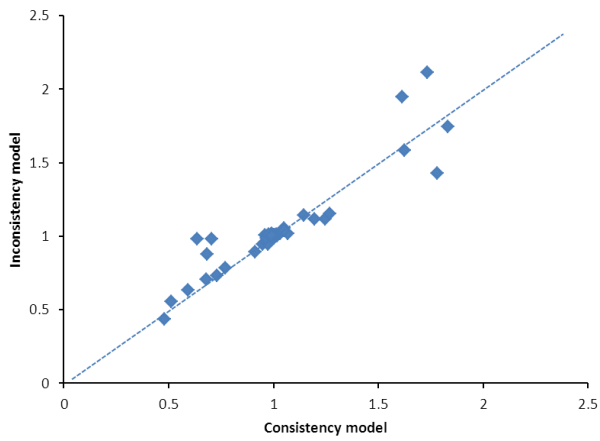


FIGURE A8.16 HBA1C: TRIALS WITH BASELINE PPD <5MM (END OF STUDY)

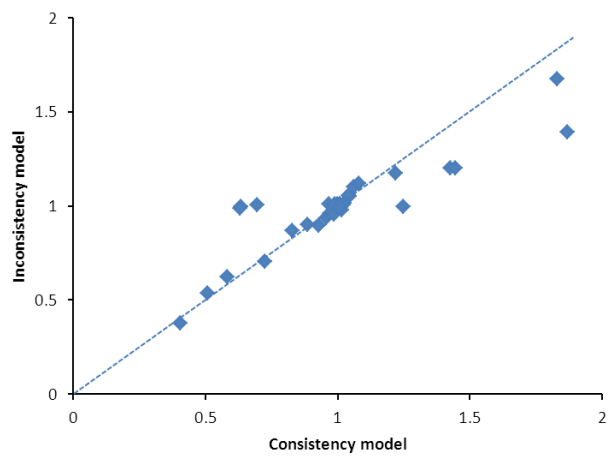


FIGURE A8.17 PPD: BASE CASE (3 MONTHS)

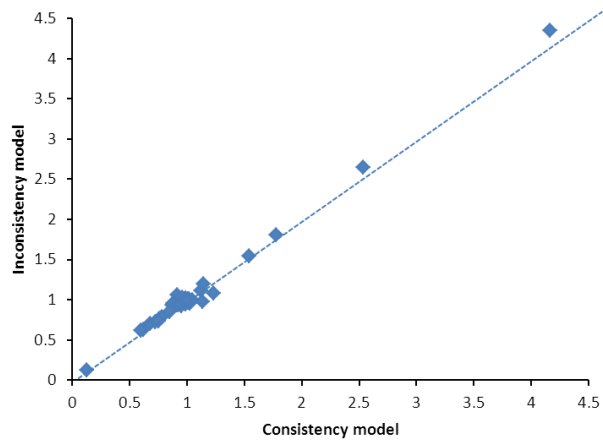


FIGURE A8.18 PPD: PARTIAL MOUTH SRP (3 MONTHS)

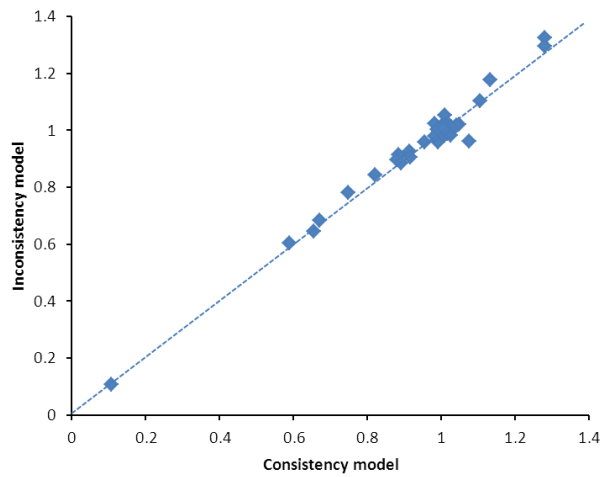


FIGURE A8.19 PPD: AGE < 65 YR (3 MONTHS)

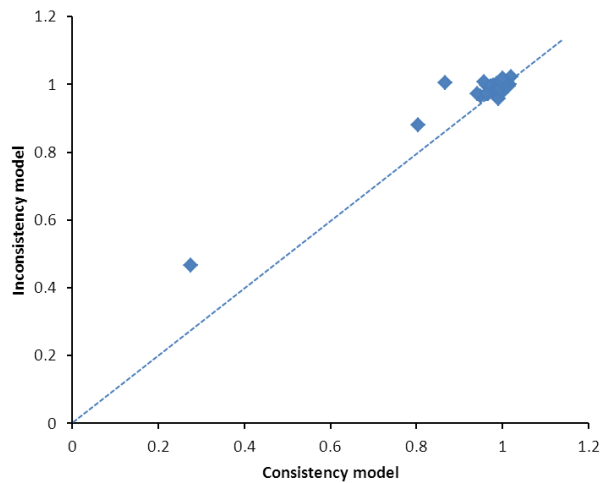


FIGURE A8.20 PPD: BASE CASE (END OF STUDY)

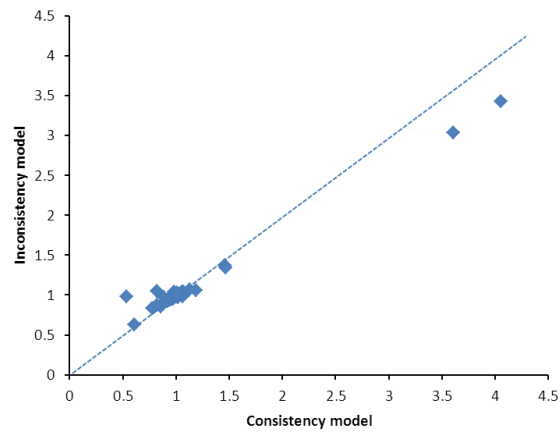


FIGURE A8.21 PPD: AGE < 65 YR (END OF STUDY)

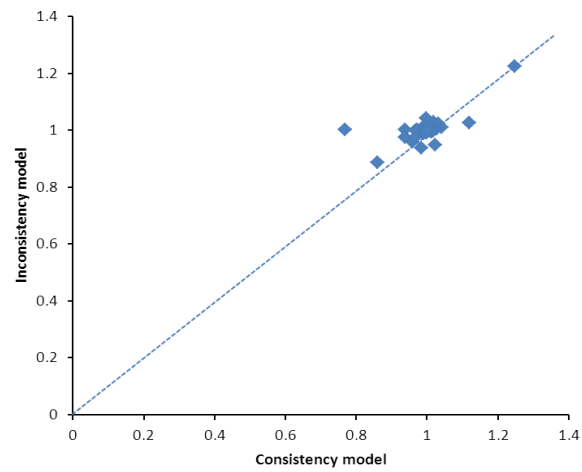


FIGURE A8.22 CAL: BASE CASE (3 MONTHS)

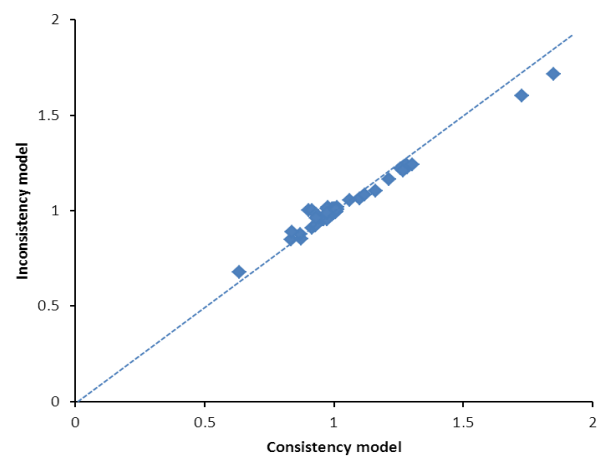


FIGURE A8.23 CAL: PARTIAL MOUTH SRP (3 MONTHS)

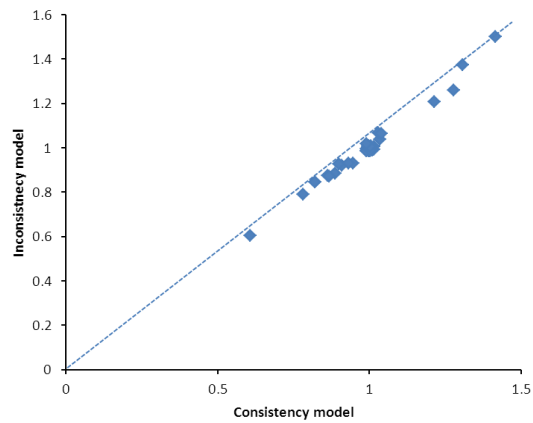


FIGURE A8.24 CAL: AGE < 65 YR (3 MONTHS)

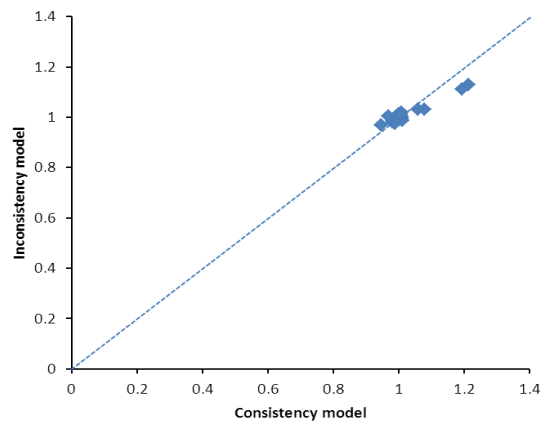


FIGURE A8.25 CAL: BASE CASE (END OF STUDY)

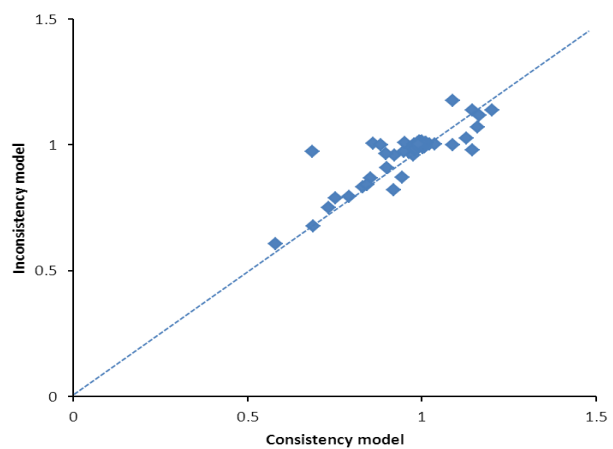


FIGURE A8.26 CAL: AGE < 65 YR (END OF STUDY)

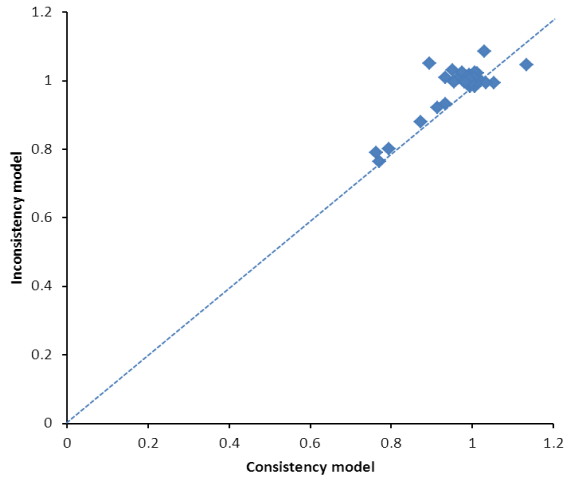


FIGURE A8.27 BOP: BASE CASE (3 MONTHS)

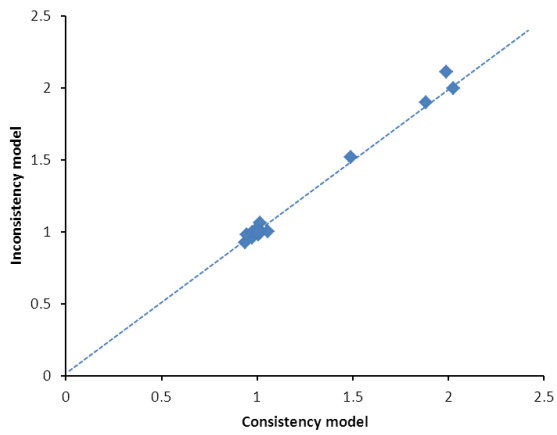


FIGURE A8.28 BOP: BASE CASE (END OF STUDY)

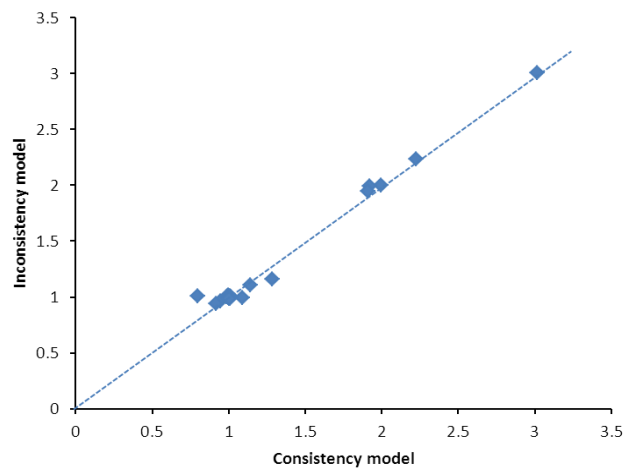


FIGURE A8.29 PI: BASE CASE (3 MONTHS)

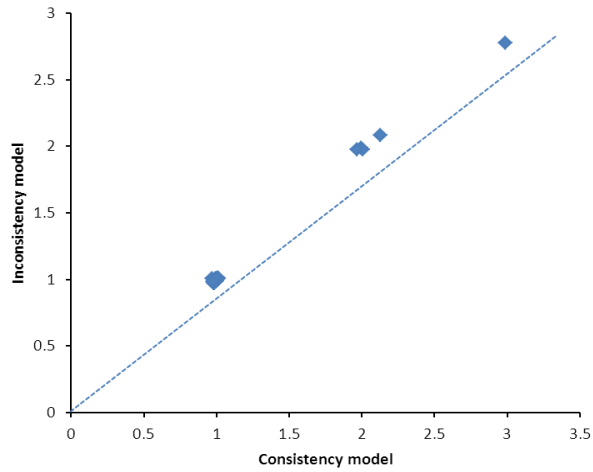


FIGURE A8.30 PI: BASE CASE (END OF STUDY)

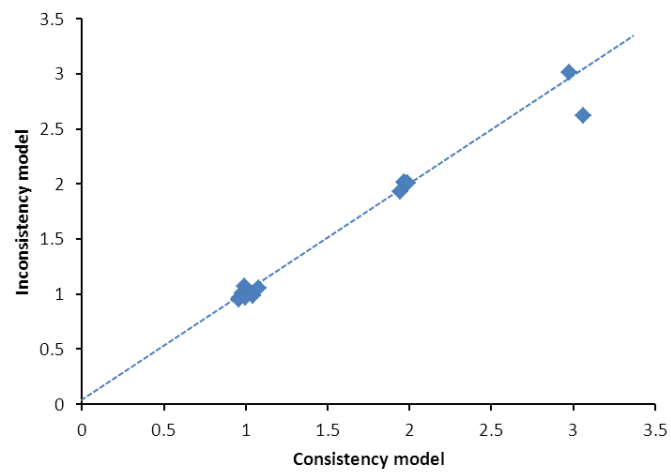


FIGURE A8.31 GI: BASE CASE (3 MONTHS)

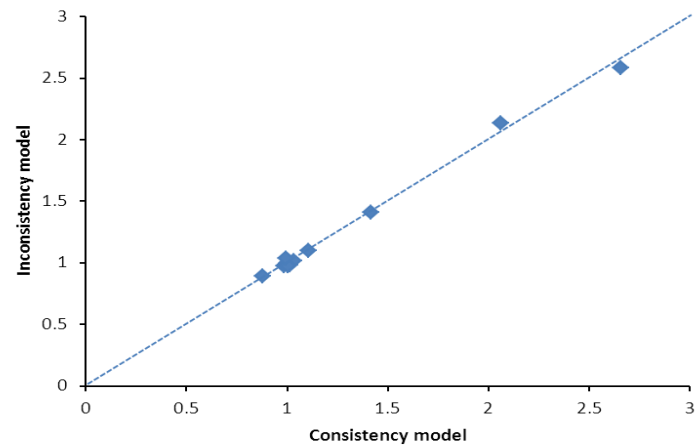


FIGURE A8.32 GI: BASE CASE (END OF STUDY)

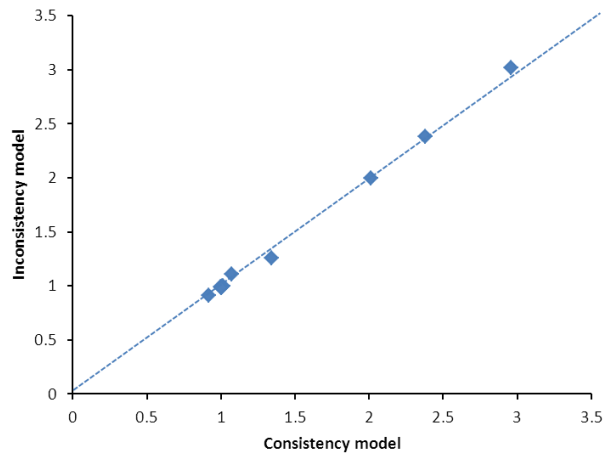
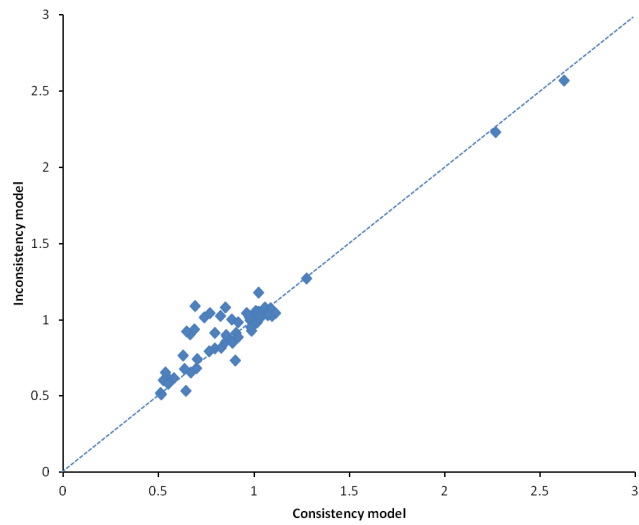


FIGURE A8.33 TOTAL WITHDRAWALS



APPENDIX 9: RESULTS FROM FIXED-EFFECTS MODEL

TABLE A9.1: HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.24* (0.06)	—											
3	0.02 (0.33)	-0.22 (0.32)	—										
4	0.02 (0.07)	0.23* (0.04)	-0.01 (0.32)	—									
5	-0.43 (0.34)	0.67* (0.34)	-0.45 (0.47)	-0.44 (0.34)	—								
6	0.8* (0.36)	0.56 (0.37)	0.78 (0.49)	0.78* (0.37)	1.22* (0.5)	—							
7	-0.08 (0.34)	-0.32 (0.34)	-0.1 (0.47)	-0.09 (0.35)	0.35 (0.48)	-0.87 (0.5)	—						
8	0.54* (0.13)	0.78* (0.12)	-0.56 (0.34)	0.55* (0.13)	-0.11 (0.36)	1.33* (0.39)	-0.46 (0.36)	—					
9	-0.16 (0.31)	-0.4 (0.31)	-0.18 (0.45)	-0.18 (0.31)	0.27 (0.46)	0.96* (0.48)	-0.09 (0.46)	0.37 (0.33)	—				
10	-0.03 (0.15)	-0.28 (0.16)	-0.05 (0.36)	-0.05 (0.17)	0.39 (0.38)	0.83* (0.4)	0.04 (0.37)	0.5* (0.2)	0.13 (0.34)	—			
11	0.26* (0.08)	0.51* (0.09)	-0.28 (0.33)	0.28* (0.1)	0.16 (0.35)	1.06* (0.37)	-0.19 (0.33)	0.27 (0.15)	-0.1 (0.32)	-0.23 (0.17)	—		
12	-0.2 (0.35)	-0.45 (0.36)	-0.22 (0.48)	-0.22 (0.36)	0.22 (0.49)	-1* (0.36)	-0.13 (0.49)	0.33 (0.38)	-0.04 (0.47)	-0.17 (0.38)	0.06 (0.36)	—	
13	0.12 (0.3)	-0.12 (0.31)	0.1 (0.45)	0.11 (0.31)	0.55 (0.46)	-0.68 (0.48)	0.2 (0.46)	0.66* (0.33)	0.28 (0.43)	0.16 (0.34)	0.38 (0.31)	0.32 (0.46)	—
14	0.28* (0.08)	0.04 (0.1)	0.26 (0.34)	0.26* (0.1)	0.71* (0.35)	-0.52 (0.37)	0.36 (0.35)	0.82* (0.15)	0.44 (0.32)	0.31 (0.17)	0.54* (0.11)	0.48 (0.36)	0.16 (0.31)
15	0.19* (0.06)	0.43* (0.08)	-0.21 (0.33)	-0.2* (0.09)	0.24 (0.35)	0.99* (0.37)	-0.11 (0.34)	0.35* (0.14)	-0.03 (0.31)	-0.15 (0.16)	0.08 (0.1)	0.02 (0.36)	-0.31 (0.31)
16	0.98* (0.36)	1.22* (0.36)	-1* (0.48)	0.99* (0.36)	0.55* (0.11)	1.78* (0.51)	-0.9 (0.49)	-0.44 (0.38)	-0.82 (0.47)	0.94* (0.39)	-0.71 (0.37)	-0.77 (0.5)	-1.1* (0.47)
17	1.58* (0.6)	1.82* (0.6)	-1.6* (0.68)	1.59* (0.6)	-1.15 (0.5)	2.38* (0.7)	-1.5* (0.69)	-1.04 (0.61)	1.42* (0.67)	1.54* (0.62)	1.32* (0.6)	1.38* (0.69)	-1.7* (0.67)
18	-0.08 (0.64)	-0.32 (0.64)	-0.1 (0.72)	-0.09 (0.65)	0.35 (0.55)	-0.88 (0.74)	0 (0.73)	0.46 (0.66)	0.08 (0.71)	-0.04 (0.66)	0.18 (0.65)	0.12 (0.73)	-0.2 (0.71)
19	2.04* (0.68)	2.28* (0.68)	2.06* (0.75)	2.06* (0.68)	1.61* (0.59)	2.84* (0.77)	1.96* (0.76)	-1.5* (0.69)	1.88* (0.74)	2.01* (0.7)	1.78* (0.68)	1.84* (0.76)	2.16* (0.74)
20	-0.12 (0.06)	0.36* (0.02)	-0.14 (0.32)	0.13* (0.05)	0.31 (0.34)	0.92* (0.37)	-0.04 (0.34)	0.42* (0.12)	0.04 (0.31)	-0.08 (0.17)	0.15 (0.1)	0.09 (0.36)	-0.24 (0.31)
21	0.18* (0.08)	0.42* (0.06)	-0.2 (0.32)	0.19* (0.06)	0.25 (0.35)	0.98* (0.37)	-0.1 (0.35)	0.36* (0.13)	-0.02 (0.32)	-0.14 (0.17)	0.08 (0.11)	0.02 (0.36)	-0.3 (0.31)

22	0.01 (0.03)	- 0.23* (0.06)	-0.01 (0.33)	-0.01 (0.07)	0.44 (0.34)	- 0.79* (0.37)	0.09 (0.34)	0.55* (0.13)	0.17 (0.31)	0.04 (0.16)	0.27* (0.08)	0.21 (0.35)	-0.11 (0.3)
23	-0.01 (0.09)	- 0.25* (0.11)	-0.03 (0.34)	-0.03 (0.12)	0.41 (0.36)	- 0.81* (0.38)	0.06 (0.35)	0.52* (0.16)	0.15 (0.32)	0.02 (0.18)	0.25* (0.12)	0.19 (0.36)	-0.13 (0.32)
24	0.14 (0.2)	-0.1 (0.19)	0.12 (0.37)	0.13 (0.19)	0.57 (0.39)	-0.66 (0.41)	0.22 (0.39)	0.68* (0.22)	0.3 (0.37)	0.18 (0.25)	0.4 (0.21)	0.34 (0.4)	0.02 (0.36)
25	-0.05 (0.15)	- 0.29* (0.14)	-0.07 (0.34)	-0.07 (0.14)	0.38 (0.37)	- 0.85* (0.39)	0.03 (0.37)	0.49* (0.18)	0.11 (0.34)	-0.02 (0.21)	0.21 (0.17)	0.15 (0.38)	-0.17 (0.34)
T	14	15	16	17	18	19	20	21	22	23	24	25	
14	—												
15	- 0.47* (0.1)	—											
16	- 1.26* (0.37)	- 0.79* (0.36)	—										
17	- 1.86* (0.6)	- 1.39* (0.6)	-0.6 (0.49)	—									
18	-0.36 (0.65)	0.11 (0.65)	0.9 (0.53)	1.5* (0.72)	—								
19	- 2.32* (0.68)	- 1.85* (0.68)	-1.06 (0.58)	-0.46 (0.32)	- 1.96* (0.79)	—							
20	-0.4* (0.1)	0.07 (0.08)	0.86* (0.36)	1.46* (0.6)	-0.04 (0.64)	1.92* (0.68)	—						
21	- 0.46* (0.11)	0.01 (0.1)	0.8* (0.36)	1.4* (0.6)	-0.1 (0.65)	1.86* (0.68)	-0.06 (0.06)	—					
22	- 0.27* (0.08)	0.2* (0.06)	0.99* (0.36)	1.59* (0.6)	0.09 (0.65)	2.05* (0.68)	0.13 (0.07)	0.19* (0.08)	—				
23	- 0.29* (0.12)	0.18 (0.11)	0.97* (0.37)	1.57* (0.61)	0.07 (0.65)	2.03* (0.69)	0.11 (0.11)	0.17 (0.12)	-0.02 (0.1)	—			
24	-0.14 (0.21)	0.33 (0.21)	1.12* (0.4)	1.72* (0.63)	0.22 (0.67)	2.18* (0.7)	0.26 (0.19)	0.32 (0.2)	0.13 (0.2)	0.15 (0.22)	—		
25	- 0.33* (0.17)	0.14 (0.16)	0.93* (0.38)	1.53* (0.62)	0.03 (0.66)	1.99* (0.69)	0.07 (0.14)	0.13 (0.13)	-0.06 (0.15)	-0.04 (0.17)	-0.19 (0.23)	—	

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 10. SRP | 14. SRP + Omega 3 + aspirin |
| 11. Control/no treatment | 15. SRP + aPDT |
| 12. Intensive OHI | 16. SRP + intensive maintenance |
| 13. CHX rinse | 17. SRP + Doxy+ intensive maintenance |
| 14. Supragingival cleaning | 18. SRP + AMX+ intensive maintenance |
| 15. Supragingival cleaning + AZM | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 16. Doxy | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 17. OHI+ SRP | 21. SRP + CHX rinse |
| 18. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 19. SRP + SDD | 23. SRP + TET (topical) |
| 20. SRP + Doxy | 24. SRP + TET (topical) + intensive maintenance |
| 21. SRP + AZM | 25. SRP + CHX rinse + Doxy |
| 22. SRP + MTZ + AMX | |

TABLE A9.2: HBA1C ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10
1	—									
2	0.25* (0.06)	—								
3	-0.13 (0.33)	-0.38 (0.32)	—							
4	-0.01 (0.07)	-0.25* (0.04)	0.13 (0.33)	—						
5	0.24 (0.19)	0 (0.19)	0.38 (0.38)	0.25 (0.2)	—					
6	0.11 (0.36)	-0.14 (0.36)	0.24 (0.49)	0.12 (0.37)	-0.14 (0.41)	—				
7	-0.06 (0.34)	-0.31 (0.34)	0.07 (0.48)	-0.05 (0.34)	-0.3 (0.39)	-0.17 (0.49)	—			
8	-0.16 (0.31)	-0.4 (0.31)	-0.02 (0.45)	-0.15 (0.31)	-0.4 (0.36)	-0.27 (0.47)	-0.1 (0.46)	—		
9	-0.14 (0.2)	-0.38 (0.2)	0 (0.39)	-0.13 (0.21)	-0.38 (0.27)	-0.24 (0.41)	-0.08 (0.39)	0.02 (0.36)	—	
10	-0.25* (0.08)	-0.5* (0.09)	-0.12 (0.34)	-0.24* (0.1)	-0.49* (0.21)	-0.36 (0.37)	-0.19 (0.33)	-0.09 (0.32)	-0.11 (0.21)	—
11	-0.59 (0.38)	-0.84* (0.39)	-0.46 (0.5)	-0.59 (0.39)	-0.84 (0.43)	-0.7* (0.35)	-0.53 (0.51)	-0.44 (0.49)	-0.46 (0.43)	-0.34 (0.39)
12	-0.2 (0.73)	-0.45 (0.73)	-0.07 (0.8)	-0.2 (0.74)	-0.45 (0.76)	-0.31 (0.81)	-0.14 (0.81)	-0.05 (0.79)	-0.07 (0.76)	0.05 (0.73)
13	-0.02 (0.09)	-0.27* (0.1)	0.11 (0.34)	-0.01 (0.11)	-0.26 (0.21)	-0.13 (0.37)	0.04 (0.35)	0.14 (0.32)	0.12 (0.21)	0.23* (0.12)
14	-0.19* (0.06)	-0.43* (0.08)	-0.05 (0.34)	-0.18* (0.09)	-0.43* (0.2)	-0.3 (0.36)	-0.13 (0.34)	-0.03 (0.31)	-0.05 (0.2)	0.06 (0.1)
15	-0.27 (0.16)	-0.52* (0.16)	-0.14 (0.36)	-0.26 (0.16)	-0.51* (0.16)	-0.38 (0.39)	-0.21 (0.37)	-0.11 (0.35)	-0.13 (0.24)	-0.02 (0.18)
16	-0.4* (0.2)	-0.65* (0.2)	-0.27 (0.38)	-0.39 (0.2)	-0.64* (0.23)	-0.51 (0.41)	-0.34 (0.39)	-0.24 (0.37)	-0.27 (0.27)	-0.15 (0.21)
17	-0.81* (0.16)	-1.06* (0.15)	-0.68 (0.36)	-0.81* (0.16)	-1.06* (0.24)	-0.92* (0.4)	-0.75* (0.37)	-0.66 (0.34)	-0.68* (0.25)	-0.57* (0.18)
18	0.19 (0.31)	-0.06 (0.31)	0.32 (0.45)	0.19 (0.32)	-0.06 (0.35)	0.08 (0.47)	0.25 (0.46)	0.34 (0.43)	0.32 (0.31)	0.43 (0.32)
19	-0.87 (0.52)	-1.12* (0.52)	-0.74 (0.61)	-0.86 (0.52)	-1.11* (0.52)	-0.98 (0.63)	-0.81 (0.62)	-0.71 (0.6)	-0.73 (0.55)	-0.62 (0.52)
20	0.63 (0.55)	0.38 (0.55)	0.76 (0.64)	0.63 (0.55)	0.38 (0.56)	0.52 (0.66)	0.69 (0.65)	0.78 (0.63)	0.76 (0.58)	0.88 (0.56)
21	0.56 (0.45)	0.32 (0.45)	0.7 (0.55)	0.57 (0.45)	0.32 (0.45)	0.45 (0.58)	0.62 (0.56)	0.72 (0.54)	0.7 (0.49)	0.81 (0.46)
22	-1.33* (0.61)	-1.58* (0.61)	-1.2 (0.69)	-1.33* (0.61)	-1.58* (0.61)	-1.44* (0.7)	-1.27 (0.69)	-1.18 (0.68)	-1.2 (0.63)	-1.08 (0.61)
23	-0.11 (0.06)	-0.36* (0.02)	0.02 (0.33)	-0.11* (0.05)	-0.36 (0.19)	-0.22 (0.37)	-0.05 (0.34)	0.04 (0.31)	0.02 (0.21)	0.14 (0.09)
24	-0.34* (0.09)	-0.58* (0.07)	-0.2 (0.32)	-0.33* (0.07)	-0.58* (0.2)	-0.44 (0.37)	-0.28 (0.35)	-0.18 (0.32)	-0.2 (0.21)	-0.09 (0.11)
25	0.02 (0.03)	-0.23* (0.06)	0.15 (0.33)	0.03 (0.08)	-0.22 (0.2)	-0.09 (0.36)	0.08 (0.34)	0.18 (0.31)	0.16 (0.2)	0.27* (0.08)
26	-0.01 (0.1)	-0.26* (0.11)	0.12 (0.34)	0 (0.12)	-0.25 (0.22)	-0.12 (0.37)	0.05 (0.35)	0.15 (0.32)	0.13 (0.22)	0.24 (0.12)
27	0.05 (0.18)	-0.2 (0.17)	0.18 (0.37)	0.05 (0.18)	-0.2 (0.26)	-0.06 (0.4)	0.11 (0.38)	0.2 (0.35)	0.18 (0.26)	0.3 (0.19)
28	-0.05 (0.54)	-0.29 (0.54)	0.09 (0.63)	-0.04 (0.54)	-0.29 (0.55)	-0.15 (0.65)	0.01 (0.63)	0.11 (0.62)	0.09 (0.57)	0.2 (0.54)
29	0.32* (0.14)	0.07 (0.13)	0.45 (0.35)	0.32* (0.13)	0.07 (0.23)	0.21 (0.39)	0.38 (0.36)	0.47 (0.34)	0.45 (0.24)	0.57* (0.15)

30	-0.21 (0.15)	-0.45* (0.14)	-0.07 (0.34)	-0.2 (0.14)	-0.45 (0.24)	-0.32 (0.39)	-0.15 (0.37)	-0.05 (0.34)	-0.07 (0.25)	0.04 (0.17)
T	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.39 (0.82)	—								
13	0.57 (0.39)	0.18 (0.74)	—							
14	0.41 (0.39)	0.02 (0.73)	-0.17 (0.1)	—						
15	0.32 (0.41)	-0.07 (0.75)	-0.25 (0.18)	-0.08 (0.17)	—					
16	0.19 (0.43)	-0.2 (0.76)	-0.38 (0.22)	-0.21 (0.21)	-0.13 (0.19)	—				
17	-0.22 (0.41)	-0.61 (0.75)	-0.8* (0.18)	-0.63* (0.17)	-0.54* (0.22)	-0.41 (0.25)	—			
18	0.78 (0.49)	0.39 (0.8)	0.2 (0.32)	0.37 (0.32)	0.46 (0.32)	0.59 (0.36)	1* (0.35)	—		
19	-0.28 (0.64)	-0.67 (0.9)	-0.85 (0.52)	-0.68 (0.52)	-0.6 (0.49)	-0.47 (0.53)	-0.06 (0.54)	-1.06 (0.59)	—	
20	1.22 (0.67)	0.83 (0.92)	0.65 (0.56)	0.81 (0.56)	0.9 (0.53)	1.03 (0.56)	1.44* (0.57)	0.44 (0.62)	1.5* (0.72)	—
21	1.16* (0.59)	0.76 (0.86)	0.58 (0.46)	0.75 (0.45)	0.83* (0.42)	0.96* (0.46)	1.38* (0.47)	0.38 (0.53)	1.43* (0.65)	-0.06 (0.68)
22	-0.74 (0.72)	-1.13 (0.95)	-1.31* (0.61)	-1.15 (0.61)	-1.06 (0.59)	-0.93 (0.61)	-0.52 (0.62)	-1.52* (0.67)	-0.46 (0.32)	-1.96* (0.79)
23	0.48 (0.39)	0.09 (0.73)	-0.09 (0.11)	0.07 (0.08)	0.16 (0.16)	0.29 (0.2)	0.7* (0.15)	-0.3 (0.31)	0.76 (0.52)	-0.74 (0.55)
24	0.26 (0.39)	-0.13 (0.74)	-0.32* (0.12)	-0.15 (0.11)	-0.07 (0.17)	0.06 (0.21)	0.48* (0.17)	-0.52 (0.32)	0.53 (0.52)	-0.96 (0.56)
25	0.61 (0.38)	0.22 (0.73)	0.04 (0.09)	0.21* (0.06)	0.29 (0.16)	0.42* (0.2)	0.83* (0.16)	-0.16 (0.31)	0.89 (0.52)	-0.61 (0.55)
26	0.58 (0.39)	0.19 (0.74)	0.01 (0.13)	0.18 (0.11)	0.26 (0.19)	0.39 (0.22)	0.81* (0.19)	-0.19 (0.32)	0.86 (0.52)	-0.64 (0.56)
27	0.64 (0.42)	0.25 (0.75)	0.07 (0.2)	0.23 (0.19)	0.32 (0.23)	0.45 (0.26)	0.86* (0.23)	-0.14 (0.36)	0.92 (0.54)	-0.58 (0.58)
28	0.55 (0.66)	0.16 (0.9)	-0.03 (0.54)	0.14 (0.54)	0.22 (0.53)	0.35 (0.5)	0.77 (0.56)	-0.23 (0.61)	0.82 (0.72)	-0.67 (0.75)
29	0.91* (0.41)	0.52 (0.75)	0.33* (0.16)	0.5* (0.15)	0.59* (0.2)	0.72* (0.23)	1.13* (0.2)	0.13 (0.34)	1.19* (0.53)	-0.31 (0.57)
30	0.39 (0.41)	0 (0.75)	-0.19 (0.18)	-0.02 (0.16)	0.06 (0.21)	0.19 (0.24)	0.61* (0.21)	-0.39 (0.34)	0.66 (0.54)	-0.83 (0.57)
T	21	22	23	24	25	26	27	28	29	30
21	—									
22	-1.89* (0.72)	—								
23	-0.68 (0.45)	1.22* (0.61)	—							
24	-0.9* (0.45)	1 (0.61)	-0.22* (0.07)	—						
25	-0.54 (0.45)	1.35* (0.61)	0.13* (0.07)	0.36* (0.09)	—					
26	-0.57 (0.46)	1.32* (0.61)	0.1 (0.11)	0.33* (0.13)	-0.03 (0.1)	—				
27	-0.51 (0.48)	1.38* (0.63)	0.16 (0.17)	0.38* (0.18)	0.03 (0.18)	0.06 (0.2)	—			
28	-0.61 (0.68)	1.29 (0.79)	0.07 (0.54)	0.29 (0.54)	-0.07 (0.54)	-0.04 (0.55)	-0.09 (0.56)	—		
29	-0.25 (0.47)	1.65* (0.62)	0.43* (0.13)	0.65* (0.14)	0.3* (0.14)	0.33 (0.17)	0.27 (0.21)	0.36 (0.55)	—	
30	-0.77 (0.47)	1.13 (0.62)	-0.09 (0.14)	0.13 (0.13)	-0.23 (0.15)	-0.2 (0.18)	-0.25 (0.22)	-0.16 (0.55)	-0.52* (0.19)	—

T: treatment

* Statistically significant

**Legend:

- | | |
|---|---|
| 1. SRP | 16. SRP + non-intensive maintenance |
| 2. Control/no treatment | 17. OHI + SRP + intensive maintenance |
| 3. Intensive OHI | 18. SRP + SDD + intensive maintenance |
| 4. CHX rinse | 19. SRP + Doxy + intensive maintenance |
| 5. Supragingival cleaning | 20. SRP + AMX + intensive maintenance |
| 6. Supragingival cleaning + AZM | 21. SRP + MTZ + AMX + intensive maintenance |
| 7. Doxy | 22. SRP + Doxy + aPDT + intensive maintenance |
| 8. SRP + powered subgingival water irrigation | 23. SRP/flap surgery+ Tinidazole + Ampicillin |
| 9. SRP + SDD | 24. SRP + CHX rinse |
| 10. SRP + Doxy | 25. SRP + SMV gel |
| 11. SRP + AZM | 26. SRP + TET (topical) |
| 12. SRP + ALN | 27. SRP + TET (topical) + intensive maintenance |
| 13. SRP + Omega 3 + aspirin | 28. SRP + TET (topical) + non-intensive maintenance |
| 14. SRP + aPDT | 29. SRP + CHX rinse + intensive maintenance |
| 15. SRP + intensive maintenance | 30. SRP + CHX rinse + Doxy |

TABLE A9.3: PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.37* (0.04)	—											
3	0.54* (0.16)	0.17 (0.16)	—										
4	0.14* (0.05)	- 0.23* (0.03)	-0.4* (0.16)	—									
5	0.01 (0.13)	0.35* (0.13)	- 0.52* (0.21)	-0.13 (0.13)	—								
6	-0.1 (0.09)	- 0.46* (0.1)	- 0.63* (0.19)	- 0.24* (0.11)	-0.11 (0.16)	—							
7	0.38 (0.23)	0.01 (0.23)	-0.16 (0.28)	0.24 (0.23)	0.36 (0.26)	0.47 (0.25)	—						
8	- 0.45* (0.06)	- 0.82* (0.04)	- 0.99* (0.17)	- 0.59* (0.05)	- 0.47* (0.14)	- 0.36* (0.11)	- 0.83* (0.23)	—					
9	-0.07 (0.13)	0.44* (0.14)	- 0.61* (0.21)	-0.21 (0.14)	-0.08 (0.19)	0.03 (0.16)	-0.45 (0.26)	0.38* (0.15)	—				
10	-0.08 (0.08)	0.45* (0.09)	- 0.62* (0.18)	- 0.22* (0.09)	-0.1 (0.15)	0.01 (0.12)	-0.46 (0.24)	0.37* (0.1)	-0.01 (0.16)	—			
11	0.1 (0.06)	0.27* (0.07)	- 0.44* (0.17)	-0.04 (0.07)	0.08 (0.14)	0.19 (0.11)	-0.28 (0.22)	0.55* (0.08)	0.17 (0.15)	0.18 (0.1)	—		
12	-0.3* (0.1)	- 0.67* (0.11)	- 0.84* (0.19)	- 0.44* (0.11)	-0.31 (0.16)	-0.2* (0.09)	- 0.67* (0.25)	0.15 (0.11)	-0.23 (0.17)	-0.22 (0.13)	- 0.39* (0.12)	—	
13	-0.4* (0.1)	0.77* (0.1)	- 0.94* (0.19)	- 0.54* (0.11)	- 0.41* (0.16)	-0.3* (0.13)	- 0.77* (0.25)	0.05 (0.11)	- 0.33* (0.17)	- 0.32* (0.12)	-0.5* (0.11)	-0.1 (0.14)	—
14	-0.9* (0.17)	- 1.27* (0.18)	- 1.44* (0.24)	- 1.04* (0.18)	- 0.91* (0.22)	-0.8* (0.2)	- 1.28* (0.28)	- 0.45* (0.18)	- 0.83* (0.22)	- 0.82* (0.19)	-1* (0.18)	-0.6* (0.2)	-0.5* (0.2)
15	0.11 (0.11)	0.26* (0.11)	- 0.43* (0.2)	-0.03 (0.12)	0.09 (0.17)	0.2 (0.14)	-0.27 (0.24)	0.56* (0.12)	0.18 (0.17)	0.19 (0.13)	0.01 (0.1)	0.41* (0.14)	0.51* (0.14)
16	- 0.97*	- 1.34*	- 1.51*	- 1.11*	- 0.99*	- 0.88*	- 1.35*	- 0.52*	-0.9* (0.16)	- 0.89*	- 1.07*	- 0.68*	- 0.57*

	(0.09)	(0.08)	(0.18)	(0.08)	(0.15)	(0.13)	(0.24)	(0.09)		(0.12)	(0.1)	(0.13)	(0.13)
17	0.01 (0.06)	- 0.36* (0.04)	- 0.53* (0.15)	- 0.13* (0.05)	-0.01 (0.14)	0.1 (0.11)	-0.37 (0.23)	0.46* (0.06)	0.08 (0.15)	0.09 (0.1)	-0.09 (0.08)	0.3* (0.11)	0.41* (0.11)
18	-1.3* (0.04)	1.67* (0.06)	1.84* (0.17)	1.44* (0.06)	1.31* (0.14)	-1.2* (0.1)	1.68* (0.23)	0.85* (0.07)	1.23* (0.14)	1.22* (0.09)	-1.4* (0.07)	-1* (0.1)	-0.9* (0.1)
19	- 0.73* (0.12)	-1.1* (0.13)	- 1.27* (0.2)	- 0.87* (0.13)	- 0.74* (0.18)	- 0.63* (0.15)	- 1.11* (0.26)	- 0.28* (0.13)	- 0.66* (0.18)	- 0.65* (0.14)	- 0.82* (0.13)	- 0.43* (0.15)	- 0.33* (0.15)
20	-0.27 (0.2)	- 0.64* (0.2)	- 0.81* (0.26)	- 0.41* (0.21)	-0.28 (0.24)	-0.17 (0.22)	- 0.65* (0.3)	0.18 (0.21)	-0.2 (0.24)	-0.19 (0.21)	-0.37 (0.21)	0.03 (0.22)	0.13 (0.22)
21	- 1.11* (0.37)	- 1.48* (0.37)	- 1.65* (0.4)	- 1.25* (0.37)	- 1.12* (0.39)	- 1.01* (0.38)	- 1.49* (0.43)	-0.66 (0.37)	- 1.04* (0.39)	- 1.03* (0.38)	- 1.21* (0.37)	- 0.81* (0.38)	-0.71 (0.38)
22	- 1.31* (0.32)	- 1.68* (0.32)	- 1.85* (0.36)	- 1.45* (0.32)	- 1.32* (0.34)	- 1.21* (0.33)	- 1.69* (0.39)	- 0.86* (0.32)	- 1.24* (0.34)	- 1.23* (0.33)	- 1.41* (0.32)	- 1.01* (0.33)	- 0.91* (0.33)
23	- 1.01* (0.12)	- 1.38* (0.12)	- 1.55* (0.2)	- 1.15* (0.13)	- 1.03* (0.18)	- 0.91* (0.15)	- 1.39* (0.26)	- 0.56* (0.13)	- 0.94* (0.18)	- 0.93* (0.14)	- 1.11* (0.13)	- 0.71* (0.15)	- 0.61* (0.15)
24	0.15 (0.1)	- 0.21* (0.11)	- 0.38* (0.19)	0.01 (0.11)	0.14 (0.17)	0.25 (0.14)	-0.22 (0.25)	0.61* (0.12)	0.22 (0.17)	0.24 (0.13)	0.06 (0.12)	0.45* (0.14)	0.55* (0.14)
25	-0.23 (0.17)	-0.6* (0.17)	- 0.77* (0.23)	- 0.37* (0.17)	-0.25 (0.21)	-0.14 (0.2)	- 0.61* (0.28)	0.22 (0.17)	-0.16 (0.22)	-0.15 (0.19)	-0.33 (0.18)	0.06 (0.2)	0.17 (0.2)
26	-0.08 (0.12)	- 0.45* (0.11)	- 0.62* (0.19)	-0.22 (0.11)	-0.1 (0.17)	0.01 (0.15)	-0.46 (0.25)	0.37* (0.12)	-0.01 (0.18)	0 (0.14)	-0.18 (0.13)	0.21 (0.15)	0.32* (0.15)
T	14	15	16	17	18	19	20	21	22	23	24	25	26
14	—												
15	1.01* (0.2)	—											
16	-0.07 (0.19)	- 1.08* (0.14)	—										
17	0.91* (0.18)	-0.1 (0.12)	0.98* (0.09)	—									
18	-0.4* (0.18)	- 1.41* (0.11)	- 0.33* (0.09)	- 1.31* (0.07)	—								
19	0.17 (0.21)	- 0.84* (0.16)	0.24 (0.15)	- 0.74* (0.13)	0.57* (0.13)	—							
20	0.63* (0.27)	-0.38 (0.23)	0.7* (0.22)	-0.28 (0.21)	1.03* (0.2)	0.46* (0.23)	—						
21	-0.21 (0.41)	- 1.22* (0.38)	-0.14 (0.38)	- 1.12* (0.37)	0.19 (0.37)	-0.38 (0.39)	- 0.84* (0.42)	—					
22	-0.41 (0.36)	- 1.42* (0.34)	-0.34 (0.33)	- 1.32* (0.32)	-0.01 (0.32)	-0.58 (0.34)	- 1.04* (0.38)	-0.2 (0.49)	—				
23	-0.11 (0.21)	- 1.12* (0.16)	-0.04 (0.15)	- 1.02* (0.13)	0.29* (0.12)	-0.28 (0.17)	- 0.74* (0.23)	0.1 (0.39)	0.3 (0.34)	—			
24	1.05* (0.2)	0.05 (0.15)	1.13* (0.13)	0.15 (0.12)	1.45* (0.11)	0.88* (0.16)	0.42 (0.22)	1.26* (0.38)	1.46* (0.33)	1.16* (0.15)	—		
25	0.67* (0.24)	-0.34 (0.2)	0.74* (0.18)	-0.24 (0.17)	1.07* (0.18)	0.5* (0.21)	0.04 (0.26)	0.88* (0.41)	1.08* (0.36)	0.78* (0.21)	-0.39 (0.2)	—	
26	0.82* (0.21)	-0.19 (0.16)	0.89* (0.13)	-0.09 (0.1)	1.22* (0.12)	0.64* (0.17)	0.19 (0.23)	1.03* (0.39)	1.23* (0.34)	0.93* (0.17)	-0.24 (0.15)	0.15 (0.2)	—

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 11. SRP | 14. SRP + Omega 3 + aspirin |
| 12. Control/no treatment | 15. SRP + aPDT |
| 13. Intensive OHI | 16. SRP/flap surgery+ Tinidazole + Ampicillin |
| 14. CHX rinse | 17. SRP + CHX rinse |
| 15. Supragingival cleaning | 18. SRP + SZ gel |
| 16. Supragingival cleaning + AZM | 19. SRP + AV gel |
| 17. Doxy | 20. SRP + AZM gel |
| 18. OHI + SRP | 21. SRP + ALN gel |
| 19. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 20. SRP + SDD | 23. SRP + CLM gel |
| 21. SRP + Doxy | 24. SRP + TET (topical) |
| 22. SRP + AZM | 25. SRP + TET (topical) + intensive maintenance |
| 23. SRP + MTZ + AMX | 26. SRP + CHX rinse + Doxy |

TABLE A9.4: PPD ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	0.4* (0.05)	—										
3	0.49* (0.17)	0.09 (0.17)	—									
4	0.17* (0.06)	-0.23* (0.03)	-0.32 (0.17)	—								
5	0.08 (0.12)	-0.32* (0.12)	-0.41* (0.21)	-0.09 (0.13)	—							
6	0.1 (0.11)	-0.3* (0.12)	-0.39 (0.2)	-0.07 (0.12)	0.02 (0.16)	—						
7	0.3 (0.23)	-0.1 (0.23)	-0.19 (0.28)	0.13 (0.23)	0.22 (0.26)	0.2 (0.25)	—					
8	-0.07 (0.13)	-0.47* (0.14)	-0.56* (0.22)	-0.24 (0.15)	-0.15 (0.18)	-0.17 (0.17)	-0.37 (0.26)	—				
9	-0.37* (0.08)	-0.76* (0.09)	-0.85* (0.19)	-0.53* (0.1)	-0.44* (0.14)	-0.47* (0.13)	-0.66* (0.24)	-0.3* (0.15)	—			
10	0.02 (0.06)	-0.38* (0.08)	-0.47* (0.18)	-0.15 (0.08)	-0.06 (0.14)	-0.08 (0.12)	-0.28 (0.22)	0.09 (0.15)	0.38* (0.1)	—		
11	-0.2 (0.11)	-0.6* (0.12)	-0.69* (0.21)	-0.37* (0.12)	-0.28 (0.17)	-0.3* (0.1)	-0.5* (0.25)	-0.13 (0.17)	0.16 (0.13)	-0.22 (0.12)	—	
12	-0.42 (0.22)	-0.82* (0.23)	-0.91* (0.28)	-0.59* (0.23)	-0.5* (0.25)	-0.52* (0.25)	-0.72* (0.32)	-0.35 (0.26)	-0.06 (0.23)	-0.44 (0.23)	-0.22 (0.25)	—
13	-0.85* (0.17)	-1.25* (0.18)	-1.34* (0.25)	-1.02* (0.18)	-0.93* (0.21)	-0.95* (0.2)	-1.15* (0.28)	-0.78* (0.22)	-0.48* (0.19)	-0.87* (0.18)	-0.65* (0.2)	-0.43 (0.28)
14	0.05 (0.11)	-0.34* (0.12)	-0.43* (0.2)	-0.11 (0.12)	-0.02 (0.16)	-0.04 (0.15)	-0.24 (0.24)	0.12 (0.17)	0.42* (0.13)	0.04 (0.1)	0.26 (0.15)	0.48 (0.24)
15	-0.1 (0.09)	-0.5* (0.07)	-0.59* (0.18)	-0.27* (0.08)	-0.18 (0.14)	-0.2 (0.14)	-0.4 (0.24)	-0.03 (0.16)	0.27* (0.11)	-0.12 (0.1)	0.1 (0.14)	0.32 (0.24)
16	-0.05 (0.1)	-0.45* (0.08)	-0.54* (0.18)	-0.22* (0.09)	-0.13 (0.15)	-0.15 (0.14)	-0.35 (0.24)	0.02 (0.17)	0.32* (0.12)	-0.07 (0.11)	0.15 (0.15)	0.37 (0.24)
17	-0.47* (0.07)	-0.87* (0.04)	-0.96* (0.17)	-0.64* (0.05)	-0.55* (0.13)	-0.57* (0.13)	-0.77* (0.23)	-0.4* (0.15)	-0.11 (0.1)	-0.49* (0.09)	-0.27* (0.13)	-0.05 (0.23)
18	-0.4 (0.21)	-0.8* (0.21)	-0.89* (0.27)	-0.57* (0.22)	-0.48* (0.24)	-0.5* (0.24)	-0.7* (0.31)	-0.33 (0.25)	-0.03 (0.21)	-0.42 (0.22)	-0.2 (0.24)	0.02 (0.3)
19	-0.41* (0.19)	-0.8* (0.18)	-0.89* (0.25)	-0.57* (0.19)	-0.48* (0.22)	-0.5* (0.22)	-0.7* (0.29)	-0.34 (0.23)	-0.04 (0.2)	-0.42* (0.2)	-0.2 (0.22)	0.02 (0.29)
20	0 (0.19)	-0.4* (0.19)	-0.49 (0.25)	-0.17 (0.19)	-0.08 (0.22)	-0.1 (0.22)	-0.3 (0.3)	0.07 (0.23)	0.37 (0.21)	-0.02 (0.2)	0.2 (0.22)	0.42 (0.29)
21	-0.5* (0.13)	-0.9* (0.12)	-0.99* (0.21)	-0.67* (0.13)	-0.58* (0.17)	-0.6* (0.17)	-0.8* (0.26)	-0.43* (0.19)	-0.14 (0.15)	-0.52* (0.14)	-0.3 (0.17)	-0.08 (0.26)
22	-0.4 (0.22)	-0.8* (0.21)	-0.88* (0.27)	-0.57* (0.21)	-0.47 (0.24)	-0.5* (0.24)	-0.69* (0.31)	-0.33 (0.25)	-0.03 (0.23)	-0.41 (0.22)	-0.2 (0.24)	0.03 (0.31)

23	-0.94* (0.09)	-1.34* (0.08)	-1.43* (0.18)	-1.11* (0.08)	-1.02* (0.15)	-1.04* (0.14)	-1.24* (0.24)	-0.87* (0.16)	-0.58* (0.12)	-0.96* (0.11)	-0.74* (0.14)	-0.52* (0.24)
24	-0.04 (0.08)	-0.44* (0.06)	-0.53* (0.16)	-0.21* (0.06)	-0.12 (0.14)	-0.14 (0.13)	-0.34 (0.24)	0.03 (0.16)	0.32* (0.11)	-0.06 (0.1)	0.16 (0.14)	0.38 (0.23)
25	-2.48* (0.38)	-2.88* (0.39)	-2.97* (0.42)	-2.65* (0.39)	-2.56* (0.4)	-2.58* (0.4)	-2.78* (0.44)	-2.41* (0.41)	-2.12* (0.39)	-2.5* (0.39)	-2.28* (0.4)	-2.06* (0.44)
26	-0.98* (0.12)	-1.38* (0.13)	-1.47* (0.21)	-1.15* (0.14)	-1.06* (0.17)	-1.08* (0.16)	-1.28* (0.26)	-0.91* (0.18)	-0.61* (0.14)	-1* (0.13)	-0.78* (0.16)	-0.56* (0.25)
27	-2.64* (0.04)	-3.04* (0.07)	-3.13* (0.18)	-2.81* (0.07)	-2.72* (0.13)	-2.74* (0.11)	-2.94* (0.23)	-2.57* (0.14)	-2.28* (0.08)	-2.66* (0.07)	-2.44* (0.11)	-2.22* (0.22)
28	-0.74* (0.15)	-1.14* (0.16)	-1.23* (0.23)	-0.91* (0.17)	-0.82* (0.2)	-0.84* (0.19)	-1.04* (0.27)	-0.67* (0.2)	-0.37* (0.17)	-0.76* (0.16)	-0.54* (0.19)	-0.32 (0.27)
29	-0.66* (0.26)	-1.06* (0.26)	-1.15* (0.31)	-0.83* (0.27)	-0.74* (0.29)	-0.76* (0.28)	-0.96* (0.34)	-0.59* (0.29)	-0.29 (0.27)	-0.68* (0.26)	-0.46 (0.28)	-0.24 (0.34)
30	-2.2* (0.41)	-2.6* (0.41)	-2.69* (0.45)	-2.37* (0.42)	-2.28* (0.43)	-2.3* (0.42)	-2.5* (0.47)	-2.13* (0.43)	-1.84* (0.42)	-2.22* (0.41)	-2* (0.42)	-1.78* (0.47)
31	0.3* (0.11)	-0.1 (0.12)	-0.19 (0.21)	0.13 (0.13)	0.22 (0.17)	0.2 (0.15)	0 (0.25)	0.37* (0.17)	0.66* (0.13)	0.28* (0.12)	0.5* (0.15)	0.72* (0.25)
32	-0.2 (0.18)	-0.6* (0.17)	-0.69* (0.24)	-0.37* (0.17)	-0.28 (0.21)	-0.3 (0.21)	-0.5 (0.28)	-0.13 (0.22)	0.17 (0.19)	-0.22 (0.18)	0 (0.21)	0.22 (0.28)
33	-1.15* (0.29)	-1.55* (0.28)	-1.64* (0.33)	-1.32* (0.28)	-1.23* (0.31)	-1.25* (0.31)	-1.45* (0.36)	-1.08* (0.32)	-0.78* (0.29)	-1.17* (0.29)	-0.95* (0.31)	-0.73* (0.36)
34	0.15 (0.08)	-0.25* (0.06)	-0.34 (0.18)	-0.02 (0.06)	0.07 (0.14)	0.05 (0.13)	-0.14 (0.24)	0.22 (0.16)	0.52* (0.11)	0.14 (0.09)	0.35* (0.13)	0.57* (0.23)
35	-2.2* (0.31)	-2.59* (0.31)	-2.68* (0.35)	-2.36* (0.31)	-2.27* (0.33)	-2.3* (0.33)	-2.49* (0.39)	-2.13* (0.34)	-1.83* (0.32)	-2.21* (0.32)	-2* (0.33)	-1.77* (0.38)
36	-0.13 (0.13)	-0.53* (0.12)	-0.62* (0.19)	-0.3* (0.12)	-0.21 (0.17)	-0.23 (0.17)	-0.43 (0.26)	-0.06 (0.19)	0.23 (0.15)	-0.15 (0.14)	0.07 (0.17)	0.29 (0.26)
T	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	0.9* (0.2)	—										
15	0.75* (0.19)	-0.15 (0.13)	—									
16	0.8* (0.2)	-0.11 (0.14)	0.05 (0.09)	—								
17	0.38* (0.19)	-0.53* (0.12)	-0.37* (0.08)	-0.42* (0.09)	—							
18	0.45 (0.27)	-0.45 (0.24)	-0.3 (0.22)	-0.35 (0.23)	0.07 (0.22)	—						
19	0.44 (0.26)	-0.46* (0.22)	-0.31 (0.17)	-0.36 (0.19)	0.07 (0.19)	-0.01 (0.28)	—					
20	0.85* (0.26)	-0.05 (0.22)	0.1 (0.17)	0.05 (0.19)	0.47* (0.19)	0.4 (0.28)	0.41 (0.24)	—				
21	0.35 (0.22)	-0.56* (0.17)	-0.4* (0.1)	-0.45* (0.13)	-0.03 (0.13)	-0.1 (0.24)	-0.1 (0.2)	-0.5* (0.2)	—			
22	0.45 (0.28)	-0.45 (0.24)	-0.3 (0.2)	-0.35 (0.22)	0.07 (0.21)	0 (0.3)	0.01 (0.11)	-0.4 (0.26)	0.1 (0.22)	—		
23	-0.09 (0.2)	-1* (0.14)	-0.84* (0.1)	-0.89* (0.11)	-0.47* (0.09)	-0.54* (0.23)	-0.54* (0.2)	-0.94* (0.2)	-0.44* (0.14)	-0.54* (0.22)	—	
24	0.81* (0.19)	-0.1 (0.13)	0.06 (0.09)	0.01 (0.1)	0.43* (0.07)	0.36 (0.22)	0.36 (0.19)	-0.04 (0.2)	0.46* (0.14)	0.36 (0.22)	0.9* (0.1)	—
25	-1.64* (0.42)	-2.54* (0.4)	-2.38* (0.39)	-2.43* (0.39)	-2.01* (0.39)	-2.09* (0.44)	-2.08* (0.43)	-2.49* (0.43)	-1.98* (0.4)	-2.09* (0.44)	-1.54* (0.39)	-2.44* (0.39)
26	-0.13 (0.21)	-1.03* (0.16)	-0.88* (0.15)	-0.93* (0.15)	-0.51* (0.14)	-0.58* (0.24)	-0.57* (0.23)	-0.98* (0.23)	-0.48* (0.18)	-0.58* (0.25)	-0.04 (0.15)	-0.94* (0.14)
27	-1.79* (0.18)	-2.7* (0.11)	-2.54* (0.09)	-2.59* (0.1)	-2.17* (0.08)	-2.24* (0.21)	-2.24* (0.19)	-2.64* (0.2)	-2.14* (0.14)	-2.25* (0.22)	-1.7* (0.1)	-2.6* (0.09)
28	0.11 (0.23)	-0.79* (0.19)	-0.64* (0.18)	-0.69* (0.18)	-0.27 (0.17)	-0.34 (0.26)	-0.33 (0.25)	-0.74* (0.25)	-0.24 (0.2)	-0.34 (0.27)	0.2 (0.18)	-0.7* (0.17)
29	0.19 (0.31)	-0.71* (0.28)	-0.56* (0.27)	-0.61* (0.28)	-0.19 (0.27)	-0.26 (0.33)	-0.25 (0.32)	-0.66* (0.32)	-0.16 (0.29)	-0.26 (0.34)	0.28 (0.27)	-0.62* (0.27)
30	-1.35* (0.45)	-2.26* (0.42)	-2.1* (0.42)	-2.15* (0.42)	-1.73* (0.42)	-1.8* (0.46)	-1.8* (0.45)	-2.2* (0.45)	-1.7* (0.43)	-1.81* (0.46)	-1.26* (0.42)	-2.16* (0.42)

31	1.15* (0.21)	0.24 (0.15)	0.4* (0.14)	0.35* (0.15)	0.77* (0.13)	0.7* (0.24)	0.7* (0.22)	0.3 (0.22)	0.8* (0.17)	0.69* (0.24)	1.24* (0.14)	0.34* (0.14)
32	0.65* (0.25)	-0.26 (0.2)	-0.1 (0.18)	-0.15 (0.18)	0.27 (0.17)	0.2 (0.27)	0.21 (0.25)	-0.2 (0.25)	0.3 (0.21)	0.2 (0.27)	0.74* (0.18)	-0.16 (0.18)
33	-0.3 (0.33)	-1.2* (0.3)	-1.05* (0.28)	-1.1* (0.27)	-0.68* (0.28)	-0.75* (0.35)	-0.74* (0.33)	-1.15* (0.33)	-0.65* (0.3)	-0.75* (0.35)	-0.21 (0.29)	-1.11* (0.29)
34	1* (0.19)	0.1 (0.13)	0.25* (0.08)	0.2* (0.1)	0.62* (0.07)	0.55* (0.22)	0.56* (0.19)	0.15 (0.19)	0.65* (0.13)	0.55* (0.21)	1.09* (0.1)	0.19* (0.08)
35	-1.35* (0.36)	-2.25* (0.33)	-2.1* (0.3)	-2.15* (0.31)	-1.72* (0.31)	-1.8* (0.37)	-1.79* (0.35)	-2.2* (0.35)	-1.7* (0.32)	-1.8* (0.36)	-1.26* (0.32)	-2.16* (0.32)
36	0.72* (0.22)	-0.19 (0.17)	-0.03 (0.14)	-0.08 (0.15)	0.34* (0.13)	0.27 (0.24)	0.27 (0.22)	-0.13 (0.22)	0.37* (0.17)	0.27 (0.24)	0.81* (0.14)	-0.09 (0.1)
T	25	26	27	28	29	30	31	32	33	34	35	36
25	—											
26	1.5* (0.4)	—										
27	-0.16 (0.38)	-1.66* (0.13)	—									
28	1.74* (0.41)	0.24 (0.19)	1.9* (0.16)	—								
29	1.82* (0.46)	0.32 (0.29)	1.98* (0.26)	0.08 (0.3)	—							
30	0.28 (0.56)	-1.22* (0.43)	0.44 (0.41)	-1.46* (0.44)	-1.54* (0.49)	—						
31	2.78* (0.4)	1.28* (0.16)	2.94* (0.12)	1.04* (0.19)	0.96* (0.28)	2.5* (0.43)	—					
32	2.28* (0.42)	0.78* (0.21)	2.44* (0.18)	0.54* (0.23)	0.46 (0.31)	2* (0.45)	-0.5* (0.21)	—				
33	1.34* (0.48)	-0.17 (0.31)	1.49* (0.29)	-0.41 (0.32)	-0.49 (0.38)	1.05* (0.5)	-1.45* (0.31)	-0.95* (0.33)	—			
34	2.64* (0.39)	1.13* (0.14)	2.79* (0.09)	0.89* (0.17)	0.81* (0.27)	2.35* (0.42)	-0.14 (0.14)	0.35* (0.18)	1.3* (0.29)	—		
35	0.29 (0.5)	-1.22* (0.34)	0.45 (0.32)	-1.46* (0.35)	-1.54* (0.41)	0.01 (0.52)	-2.49* (0.33)	-2* (0.35)	-1.05* (0.41)	-2.35* (0.31)	—	
36	2.35* (0.4)	0.85* (0.18)	2.51* (0.14)	0.61* (0.2)	0.53 (0.29)	2.07* (0.43)	-0.43* (0.17)	0.07 (0.21)	1.02* (0.3)	-0.28* (0.13)	2.06* (0.33)	—

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 19. SRP | 19. SRP + Doxy+ intensive maintenance |
| 20. Control/no treatment | 20. SRP + AMX+ intensive maintenance |
| 21. Intensive OHI | 21. SRP + MTZ + AMX + intensive maintenance |
| 22. CHX rinse | 22. SRP+ Doxy+ aPDT + intensive maintenance |
| 23. Supragingival cleaning | 23. SRP/flap surgery+ Tinidazole + Ampicillin |
| 24. Supragingival cleaning + AZM | 24. SRP + CHX rinse |
| 25. Doxy | 25. SRP + SMV gel |
| 26. SRP + powered subgingival water irrigation | 26. SRP + CLM gel |
| 27. SRP + SDD | 27. SRP + SZ gel |
| 28. SRP + Doxy | 28. SRP + AV gel |
| 29. SRP + AZM | 29. SRP + AZM gel |
| 30. SRP + ALN | 30. SRP + ALN gel |
| 31. SRP + Omega 3 + aspirin | 31. SRP + TET (topical) |
| 32. SRP + aPDT | 32. SRP + TET (topical) + intensive maintenance |
| 33. SRP + intensive maintenance | 33. SRP + TET (topical) + non-intensive maintenance |
| 34. SRP + non-intensive maintenance | 34. SRP + CHX rinse + intensive maintenance |
| 35. OHI+ SRP+ intensive maintenance | 35. SRP + Doxy gel+ intensive maintenance |
| 36. SRP + SDD + intensive maintenance | 36. SRP + CHX rinse + Doxy |

TABLE A9.5: CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	0.44*	—											

	(0.05)												
3	0.6* (0.22)	0.16 (0.22)	—										
4	0.11 (0.11)	0.33* (0.11)	0.49* (0.24)	—									
5	0 (0.16)	0.44* (0.17)	-0.6* (0.27)	-0.11 (0.2)	—								
6	0.09 (0.64)	-0.36 (0.64)	-0.52 (0.67)	-0.03 (0.64)	0.08 (0.66)	—							
7	- 0.29* (0.07)	- 0.73* (0.05)	- 0.89* (0.22)	-0.4* (0.12)	-0.29 (0.18)	-0.37 (0.64)	—						
8	0.12 (0.22)	-0.32 (0.23)	-0.48 (0.31)	0.01 (0.25)	0.12 (0.27)	0.04 (0.67)	0.41 (0.23)	—					
9	0.08 (0.13)	0.36* (0.14)	0.52* (0.25)	-0.03 (0.17)	0.08 (0.21)	0 (0.65)	0.37* (0.15)	-0.04 (0.25)	—				
10	-0.02 (0.06)	0.46* (0.07)	0.62* (0.23)	-0.13 (0.12)	-0.02 (0.17)	-0.1 (0.63)	0.27* (0.09)	-0.14 (0.23)	-0.1 (0.14)	—			
11	-0.2 (0.15)	0.64* (0.16)	-0.8* (0.26)	-0.31 (0.18)	-0.2 (0.14)	-0.28 (0.65)	0.09 (0.17)	-0.32 (0.27)	-0.28 (0.19)	-0.18 (0.16)	—		
12	-0.3 (0.16)	0.74* (0.17)	-0.9* (0.27)	-0.41* (0.2)	-0.3 (0.23)	-0.38 (0.66)	-0.01 (0.18)	-0.42 (0.28)	-0.38 (0.21)	-0.28 (0.18)	-0.1 (0.22)	—	
13	-0.4 (0.29)	0.84* (0.29)	-1* (0.36)	-0.51 (0.31)	-0.4 (0.33)	-0.48 (0.7)	-0.11 (0.3)	-0.52 (0.36)	-0.48 (0.31)	-0.38 (0.29)	-0.2 (0.32)	-0.1 (0.33)	—
14	0.03 (0.23)	-0.41 (0.23)	-0.57 (0.31)	-0.08 (0.25)	0.03 (0.28)	-0.05 (0.67)	0.32 (0.24)	-0.09 (0.32)	-0.05 (0.26)	0.05 (0.22)	0.23 (0.27)	0.33 (0.28)	0.43 (0.37)
15	-0.14 (0.08)	0.58* (0.06)	0.74* (0.22)	0.25* (0.12)	-0.14 (0.18)	-0.22 (0.64)	0.15 (0.08)	-0.26 (0.23)	-0.22 (0.15)	-0.12 (0.09)	0.06 (0.17)	0.16 (0.18)	0.26 (0.3)
16	0.21* (0.1)	0.23* (0.09)	0.39* (0.19)	0.1 (0.14)	0.21 (0.19)	0.13 (0.64)	0.5* (0.11)	0.09 (0.24)	0.13 (0.16)	0.23* (0.11)	0.41* (0.18)	0.51* (0.19)	0.61* (0.3)
17	- 0.98* (0.02)	- 1.43* (0.06)	- 1.58* (0.22)	- 1.09* (0.11)	- 0.98* (0.17)	-1.07 (0.64)	- 0.69* (0.08)	-1.1* (0.22)	- 1.06* (0.13)	- 0.96* (0.06)	- 0.78* (0.15)	- 0.68* (0.17)	- 0.58* (0.29)
18	- 0.27* (0.09)	- 0.71* (0.1)	- 0.87* (0.24)	- 0.38* (0.14)	-0.27 (0.18)	-0.36 (0.64)	0.02 (0.11)	-0.39 (0.24)	- 0.35* (0.15)	- 0.25* (0.1)	-0.07 (0.17)	0.03 (0.19)	0.13 (0.3)
19	-0.19 (0.16)	0.64* (0.17)	0.79* (0.27)	-0.3 (0.19)	-0.19 (0.23)	-0.28 (0.66)	0.09 (0.18)	-0.31 (0.27)	-0.27 (0.2)	-0.17 (0.17)	0.01 (0.22)	0.11 (0.23)	0.21 (0.33)
20	- 1.72* (0.31)	- 2.17* (0.32)	- 2.32* (0.38)	- 1.83* (0.33)	- 1.72* (0.35)	- 1.81* (0.71)	- 1.44* (0.32)	- 1.84* (0.38)	-1.8* (0.33)	-1.7* (0.32)	- 1.52* (0.35)	- 1.42* (0.35)	- 1.32* (0.42)
21	- 1.48* (0.19)	- 1.93* (0.2)	- 2.09* (0.29)	- 1.59* (0.22)	- 1.48* (0.25)	- 1.57* (0.67)	-1.2* (0.2)	-1.6* (0.29)	- 1.56* (0.23)	- 1.46* (0.2)	- 1.28* (0.24)	- 1.18* (0.25)	- 1.08* (0.35)
22	- 0.52* (0.09)	- 0.96* (0.1)	- 1.12* (0.24)	- 0.63* (0.14)	- 0.52* (0.19)	-0.6 (0.64)	- 0.23* (0.11)	- 0.64* (0.24)	-0.6* (0.15)	-0.5* (0.1)	-0.32 (0.17)	-0.22 (0.19)	-0.12 (0.3)
23	0.13 (0.19)	-0.31 (0.2)	-0.47 (0.29)	0.02 (0.22)	0.13 (0.25)	0.05 (0.66)	0.42* (0.21)	0.01 (0.29)	0.05 (0.23)	0.15 (0.2)	0.33 (0.24)	0.43 (0.25)	0.53 (0.35)
24	0.18 (0.16)	-0.26 (0.15)	-0.42 (0.23)	0.07 (0.18)	0.18 (0.23)	0.1 (0.66)	0.47* (0.16)	0.06 (0.27)	0.1 (0.2)	0.2 (0.17)	0.38 (0.22)	0.48* (0.23)	0.58 (0.33)
T	14	15	16	17	18	19	20	21	22	23	24		
14	—												
15	-0.17	—											

	(0.24)												
16	0.18 (0.25)	0.35* (0.11)	—										
17	- 1.01* (0.23)	- 0.84* (0.08)	- 1.19* (0.1)	—									
18	-0.3 (0.24)	-0.13 (0.12)	- 0.48* (0.13)	0.71* (0.09)	—								
19	-0.22 (0.28)	-0.06 (0.18)	-0.4* (0.19)	0.79* (0.16)	0.08 (0.18)	—							
20	- 1.75* (0.39)	- 1.59* (0.32)	- 1.93* (0.33)	- 0.74* (0.31)	- 1.45* (0.32)	- 1.53* (0.35)	—						
21	- 1.51* (0.3)	- 1.35* (0.21)	- 1.69* (0.22)	-0.5* (0.19)	- 1.21* (0.21)	- 1.29* (0.25)	0.24 (0.36)	—					
22	- 0.55* (0.24)	- 0.38* (0.12)	- 0.73* (0.13)	0.46* (0.09)	- 0.25* (0.12)	-0.33 (0.18)	1.2* (0.32)	0.96* (0.21)	—				
23	0.1 (0.3)	0.27 (0.21)	-0.08 (0.22)	1.11* (0.19)	0.4 (0.21)	0.32 (0.25)	1.85* (0.36)	1.61* (0.27)	0.65* (0.21)	—			
24	0.15 (0.28)	0.32 (0.16)	-0.03 (0.12)	1.16* (0.16)	0.45* (0.18)	0.37 (0.22)	1.9* (0.35)	1.66* (0.25)	0.7* (0.18)	0.05 (0.25)	—		

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 9. SRP | 13. SRP + Omega 3 + aspirin |
| 10. Control/no treatment | 14. SRP + aPDT |
| 11. Intensive OHI | 15. SRP/flap surgery+ Tinidazole + Ampicillin |
| 12. Supragingival cleaning | 16. SRP + CHX rinse |
| 13. Supragingival cleaning + AZM | 17. SRP + SZ gel |
| 14. Doxy | 18. SRP + AV gel |
| 15. OHI + SRP | 19. SRP + AZM gel |
| 16. SRP + powered subgingival water irrigation | 20. SRP + ALN gel |
| 17. SRP + SDD | 21. SRP + SMV gel |
| 18. SRP + Doxy | 22. SRP + CLM gel |
| 19. SRP + AZM | 23. SRP + TET (topical) |
| 20. SRP + MTZ + AMX | 24. SRP + CHX rinse + Doxy |

**TABLE A9.6: CAL ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY
(MEAN±SD)**

T**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	0.55* (0.06)	—									
3	0.14 (0.11)	-0.41* (0.11)	—								
4	0.1 (0.17)	-0.45* (0.18)	-0.04 (0.21)	—							
5	0.1 (0.64)	-0.45 (0.64)	-0.04 (0.65)	0 (0.66)	—						
6	0.12 (0.22)	-0.43 (0.23)	-0.02 (0.25)	0.02 (0.28)	0.02 (0.67)	—					
7	-0.59* (0.07)	-1.15* (0.09)	-0.73* (0.14)	-0.7* (0.19)	-0.7 (0.64)	-0.72* (0.23)	—				
8	-0.02 (0.06)	-0.57* (0.08)	-0.16 (0.13)	-0.12 (0.18)	-0.12 (0.63)	-0.14 (0.23)	0.57* (0.09)	—			
9	0.1 (0.16)	-0.45* (0.17)	-0.04 (0.19)	0 (0.15)	0 (0.66)	-0.02 (0.27)	0.7* (0.17)	0.12 (0.17)	—		
10	-0.52* (0.17)	-1.07* (0.17)	-0.66* (0.17)	-0.62* (0.17)	-0.62 (0.17)	-0.64* (0.17)	0.08 (0.17)	-0.5* (0.17)	-0.62* (0.17)	—	

	(0.21)	(0.22)	(0.24)	(0.28)	(0.67)	(0.31)	(0.23)	(0.22)	(0.27)		
11	-0.65* (0.31)	-1.2* (0.32)	-0.79* (0.33)	-0.75* (0.36)	-0.75 (0.71)	-0.77* (0.38)	-0.05 (0.32)	-0.63* (0.32)	-0.75* (0.35)	-0.13 (0.38)	—
12	0.03 (0.23)	-0.52* (0.23)	-0.11 (0.25)	-0.07 (0.29)	-0.07 (0.67)	-0.09 (0.32)	0.63* (0.24)	0.05 (0.22)	-0.07 (0.28)	0.55 (0.31)	0.68 (0.39)
13	-0.03 (0.12)	-0.58* (0.12)	-0.17 (0.16)	-0.13 (0.21)	-0.13 (0.65)	-0.15 (0.25)	0.56* (0.14)	-0.01 (0.13)	-0.13 (0.2)	0.49* (0.25)	0.62 (0.33)
14	0.03 (0.16)	-0.52* (0.15)	-0.11 (0.19)	-0.08 (0.24)	-0.08 (0.66)	-0.1 (0.27)	0.62* (0.18)	0.05 (0.17)	-0.08 (0.22)	0.55* (0.27)	0.67 (0.35)
15	-0.23* (0.08)	-0.78* (0.05)	-0.37* (0.12)	-0.33 (0.19)	-0.33 (0.64)	-0.35 (0.23)	0.36* (0.11)	-0.21* (0.09)	-0.33 (0.17)	0.29 (0.23)	0.42 (0.32)
16	-0.9* (0.16)	-1.45* (0.16)	-1.04* (0.19)	-1* (0.23)	-1 (0.65)	-1.02* (0.27)	-0.3 (0.16)	-0.88* (0.17)	-1* (0.22)	-0.38 (0.27)	-0.25 (0.35)
17	-0.43 (0.36)	-0.98* (0.36)	-0.57 (0.38)	-0.53 (0.4)	-0.53 (0.73)	-0.55 (0.43)	0.17 (0.37)	-0.41 (0.37)	-0.53 (0.4)	0.09 (0.42)	0.22 (0.48)
18	-0.03 (0.32)	-0.58 (0.32)	-0.17 (0.34)	-0.13 (0.37)	-0.13 (0.71)	-0.15 (0.39)	0.56 (0.33)	-0.01 (0.33)	-0.13 (0.36)	0.49 (0.39)	0.62 (0.45)
19	-0.43* (0.21)	-0.98* (0.21)	-0.57* (0.23)	-0.53* (0.27)	-0.53 (0.67)	-0.55 (0.3)	0.16 (0.22)	-0.41 (0.22)	-0.53* (0.26)	0.09 (0.3)	0.22 (0.37)
20	-0.51 (0.42)	-1.06* (0.41)	-0.65 (0.43)	-0.61 (0.45)	-0.61 (0.76)	-0.63 (0.47)	0.09 (0.42)	-0.49 (0.42)	-0.61 (0.44)	0.01 (0.47)	0.14 (0.52)
21	-0.03 (0.08)	-0.58* (0.06)	-0.17 (0.12)	-0.13 (0.19)	-0.13 (0.64)	-0.15 (0.23)	0.56* (0.11)	-0.01 (0.1)	-0.13 (0.18)	0.49* (0.23)	0.62 (0.32)
22	-2.83* (0.35)	-3.38* (0.35)	-2.97* (0.36)	-2.93* (0.39)	-2.93* (0.72)	-2.95* (0.41)	-2.23* (0.35)	-2.81* (0.35)	-2.93* (0.38)	-2.31* (0.41)	-2.18* (0.46)
23	-0.83* (0.09)	-1.38* (0.11)	-0.97* (0.14)	-0.93* (0.2)	-0.93 (0.64)	-0.95* (0.24)	-0.24* (0.12)	-0.81* (0.11)	-0.93* (0.18)	-0.31 (0.23)	-0.18 (0.32)
24	-2.28* (0.03)	-2.83* (0.07)	-2.42* (0.12)	-2.38* (0.18)	-2.38* (0.64)	-2.4* (0.22)	-1.69* (0.08)	-2.26* (0.07)	-2.38* (0.16)	-1.76* (0.22)	-1.63* (0.31)
25	-0.6* (0.11)	-1.15* (0.12)	-0.74* (0.16)	-0.7* (0.21)	-0.7 (0.65)	-0.72* (0.24)	-0.01 (0.13)	-0.58* (0.12)	-0.7* (0.19)	-0.08 (0.24)	0.05 (0.33)
26	-0.6* (0.13)	-1.15* (0.14)	-0.74* (0.17)	-0.7* (0.22)	-0.7 (0.65)	-0.72* (0.25)	0 (0.15)	-0.58* (0.14)	-0.7* (0.2)	-0.08 (0.25)	0.05 (0.34)
27	-1.98* (0.31)	-2.53* (0.32)	-2.12* (0.33)	-2.08* (0.36)	-2.08* (0.71)	-2.1* (0.38)	-1.39* (0.32)	-1.96* (0.32)	-2.08* (0.35)	-1.46* (0.38)	-1.33* (0.44)
28	-0.18 (0.21)	-0.73* (0.21)	-0.32 (0.23)	-0.28 (0.27)	-0.28 (0.67)	-0.3 (0.3)	0.41 (0.22)	-0.16 (0.21)	-0.28 (0.26)	0.34 (0.29)	0.47 (0.37)
29	-1.15* (0.41)	-1.7* (0.41)	-1.29* (0.42)	-1.25* (0.45)	-1.25 (0.76)	-1.27* (0.47)	-0.55 (0.42)	-1.13* (0.42)	-1.25* (0.44)	-0.63 (0.47)	-0.5 (0.52)
30	0.35* (0.1)	-0.2* (0.09)	0.21 (0.14)	0.25 (0.2)	0.25 (0.64)	0.23 (0.24)	0.95* (0.12)	0.37* (0.11)	0.25 (0.19)	0.87* (0.24)	1* (0.33)
31	-2.34* (0.42)	-2.89* (0.42)	-2.48* (0.43)	-2.44* (0.46)	-2.44* (0.76)	-2.46* (0.47)	-1.74* (0.43)	-2.32* (0.43)	-2.44* (0.45)	-1.82* (0.47)	-1.69* (0.52)
T	12	13	14	15	16	17	18	19	20	21	22
12	—										
13	-0.06 (0.26)	—									
14	-0.01 (0.28)	0.06 (0.16)	—								
15	-0.26 (0.24)	-0.2 (0.13)	-0.26 (0.16)	—							
16	-0.93* (0.28)	-0.87* (0.17)	-0.92* (0.21)	-0.67* (0.17)	—						
17	-0.46 (0.43)	-0.4 (0.34)	-0.45 (0.38)	-0.2 (0.36)	0.47 (0.38)	—					
18	-0.06 (0.39)	0 (0.3)	-0.06 (0.33)	0.2 (0.32)	0.87* (0.34)	0.4 (0.45)	—				
19	-0.46 (0.31)	-0.4* (0.17)	-0.46* (0.23)	-0.2 (0.21)	0.47 (0.24)	0 (0.38)	-0.4 (0.34)	—			
20	-0.54 (0.47)	-0.48 (0.4)	-0.53 (0.43)	-0.28 (0.42)	0.39 (0.43)	-0.08 (0.2)	-0.48 (0.49)	-0.08 (0.43)	—		
21	-0.06 (0.24)	0 (0.13)	-0.06 (0.17)	0.2* (0.08)	0.87* (0.17)	0.4 (0.36)	0 (0.32)	0.4 (0.21)	0.48 (0.42)	—	

22	-2.86* (0.41)	-2.8* (0.37)	-2.85* (0.38)	-2.6* (0.35)	-1.93* (0.38)	-2.4* (0.5)	-2.8* (0.47)	-2.4* (0.4)	-2.32* (0.54)	-2.8* (0.36)	—
23	-0.86* (0.24)	-0.8* (0.15)	-0.86* (0.19)	-0.6* (0.12)	0.07 (0.18)	-0.4 (0.37)	-0.8* (0.33)	-0.4 (0.23)	-0.32 (0.42)	-0.8* (0.12)	2* (0.36)
24	-2.31* (0.23)	-2.25* (0.13)	-2.31* (0.17)	-2.05* (0.08)	-1.38* (0.16)	-1.85* (0.37)	-2.25* (0.32)	-1.85* (0.21)	-1.77* (0.42)	-2.25* (0.09)	0.55 (0.35)
25	-0.63* (0.25)	-0.57* (0.16)	-0.63* (0.2)	-0.37* (0.13)	0.3 (0.19)	-0.17 (0.38)	-0.57 (0.34)	-0.17 (0.24)	-0.09 (0.43)	-0.57* (0.14)	2.23* (0.36)
26	-0.63* (0.26)	-0.57* (0.18)	-0.62* (0.21)	-0.37* (0.15)	0.3 (0.2)	-0.17 (0.39)	-0.57 (0.35)	-0.17 (0.24)	-0.09 (0.44)	-0.57* (0.15)	2.23* (0.37)
27	-2.01* (0.38)	-1.95* (0.33)	-2.01* (0.35)	-1.75* (0.32)	-1.08* (0.35)	-1.55* (0.48)	-1.95* (0.45)	-1.55* (0.37)	-1.47* (0.52)	-1.95* (0.32)	0.85 (0.46)
28	-0.21 (0.31)	-0.15 (0.24)	-0.21 (0.26)	0.05 (0.22)	0.72* (0.26)	0.25 (0.42)	-0.15 (0.38)	0.25 (0.29)	0.33 (0.47)	-0.15 (0.22)	2.65* (0.4)
29	-1.18* (0.47)	-1.12* (0.41)	-1.17* (0.38)	-0.92* (0.41)	-0.25 (0.44)	-0.72 (0.53)	-1.12* (0.51)	-0.71 (0.44)	-0.64 (0.57)	-1.12* (0.41)	1.68* (0.54)
30	0.32 (0.25)	0.38* (0.12)	0.33 (0.17)	0.58* (0.1)	1.25* (0.18)	0.78* (0.36)	0.38 (0.32)	0.78* (0.21)	0.86* (0.42)	0.38* (0.1)	3.18* (0.36)
31	-2.37* (0.48)	-2.31* (0.4)	-2.36* (0.43)	-2.11* (0.42)	-1.44* (0.44)	-1.91* (0.53)	-2.31* (0.5)	-1.91* (0.44)	-1.83* (0.56)	-2.31* (0.42)	0.49 (0.55)
T	23	24	25	26	27	28	29	30	31		
23	—										
24	-1.45* (0.09)	—									
25	0.23 (0.14)	1.68* (0.11)	—								
26	0.23 (0.16)	1.68* (0.13)	0 (0.17)	—							
27	-1.15* (0.32)	0.3 (0.31)	-1.38* (0.33)	-1.38* (0.34)	—						
28	0.65* (0.22)	2.1* (0.21)	0.42 (0.23)	0.42 (0.24)	1.8* (0.37)	—					
29	-0.31 (0.42)	1.13* (0.41)	-0.54 (0.43)	-0.55 (0.43)	0.83 (0.51)	-0.97* (0.46)	—				
30	1.19* (0.14)	2.63* (0.11)	0.96* (0.15)	0.95* (0.16)	2.33* (0.33)	0.53* (0.23)	1.5* (0.41)	—			
31	-1.51* (0.43)	-0.06 (0.42)	-1.74* (0.44)	-1.74* (0.44)	-0.36 (0.52)	-2.16* (0.47)	-1.19* (0.57)	-2.69* (0.42)	—		

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 17. SRP | 17. SRP + Doxy+ intensive maintenance |
| 18. Control/no treatment | 18. SRP + AMX+ intensive maintenance |
| 19. Supragingival cleaning | 19. SRP + MTZ + AMX + intensive maintenance |
| 20. Supragingival cleaning + AZM | 20. SRP+ Doxy+ aPDT + intensive maintenance |
| 21. Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin |
| 22. SRP + powered subgingival water irrigation | 22. SRP + SMV gel |
| 23. SRP + SDD | 23. SRP + CLM gel |
| 24. SRP + Doxy | 24. SRP + SZ gel |
| 25. SRP + AZM | 25. SRP + AV gel |
| 26. SRP + ALN | 26. SRP + AZM gel |
| 27. SRP + Omega 3 + aspirin | 27. SRP + ALN gel |
| 28. SRP + aPDT | 28. SRP + TET (topical) |
| 29. SRP + intensive maintenance | 29. SRP + TET (topical) + non-intensive maintenance |
| 30. SRP + non-intensive maintenance | 30. SRP + CHX rinse + intensive maintenance |
| 31. OHI+ SRP+ intensive maintenance | 31. SRP + Doxy gel+ intensive maintenance |
| 32. SRP + SDD + intensive maintenance | |

TABLE A9.7: BOP ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
-----	---	---	---	---	---	---	---	---	---	----	----	----	----

1	—												
2	1.39* (0.14)	—											
3	1.22* (0.38)	-0.17 (0.36)	—										
4	0.35 (0.28)	-1.04* (0.28)	-0.88 (0.46)	—									
5	-0.2 (0.24)	-1.59* (0.27)	-1.42* (0.45)	-0.55 (0.36)	—								
6	0.73* (0.34)	-0.67 (0.37)	-0.5 (0.51)	0.38 (0.44)	0.92* (0.41)	—							
7	-1.94* (0.34)	-3.33* (0.31)	-3.17* (0.47)	-2.29* (0.42)	-1.74* (0.41)	-2.67* (0.48)	—						
8	-0.16 (0.1)	-1.56* (0.18)	-1.39* (0.4)	-0.51 (0.3)	0.03 (0.26)	-0.89* (0.36)	1.78* (0.35)	—					
9	-0.14 (0.16)	-1.53* (0.21)	-1.37* (0.41)	-0.49 (0.32)	0.06 (0.28)	-0.87* (0.3)	1.8* (0.37)	0.02 (0.19)	—				
10	-0.7* (0.25)	-2.09* (0.29)	-1.93* (0.45)	-1.05* (0.37)	-0.5* (0.25)	-1.43* (0.42)	1.24* (0.42)	-0.54* (0.27)	-0.56 (0.29)	—			
11	-1.29* (0.29)	-2.68* (0.32)	-2.51* (0.48)	-1.63* (0.4)	-1.09* (0.37)	-2.01* (0.44)	0.66 (0.44)	-1.12* (0.3)	-1.14* (0.33)	-0.58 (0.38)	—		
12	-0.29 (0.27)	-1.69* (0.31)	-1.52* (0.47)	-0.64 (0.39)	-0.1 (0.36)	-1.02* (0.44)	1.65* (0.43)	-0.13 (0.29)	-0.15 (0.31)	0.41 (0.37)	0.99* (0.4)	—	
13	0.34 (0.33)	-1.05* (0.36)	-0.88 (0.5)	0 (0.43)	0.54 (0.4)	-0.38 (0.45)	2.29* (0.47)	0.51 (0.34)	0.48 (0.33)	1.05* (0.41)	1.63* (0.44)	0.64 (0.43)	—
14	-0.78* (0.24)	-2.18* (0.2)	-2.01* (0.41)	-1.13* (0.34)	-0.59 (0.34)	-1.51* (0.42)	1.16* (0.37)	-0.62* (0.27)	-0.64* (0.29)	-0.08 (0.35)	0.5 (0.38)	-0.49 (0.37)	-1.13* (0.41)
15	0.79* (0.16)	-0.6* (0.09)	-0.43 (0.35)	0.44 (0.29)	0.99* (0.28)	0.07 (0.38)	2.73* (0.32)	0.96* (0.19)	0.93* (0.22)	1.49* (0.29)	2.08* (0.33)	1.09* (0.32)	0.45 (0.36)
16	-1* (0.27)	-2.39* (0.31)	-2.22* (0.47)	-1.35* (0.39)	-0.8* (0.36)	-1.73* (0.44)	0.94* (0.43)	-0.84* (0.29)	-0.86* (0.31)	-0.3 (0.37)	0.29 (0.39)	-0.71 (0.38)	-1.34* (0.43)
17	-0.66* (0.27)	-2.05* (0.31)	-1.88* (0.47)	-1.01* (0.39)	-0.46 (0.36)	-1.38* (0.44)	1.29* (0.43)	-0.49 (0.29)	-0.52 (0.31)	0.04 (0.37)	0.63 (0.4)	-0.36 (0.39)	-1* (0.43)
18	-0.85* (0.32)	-2.24* (0.35)	-2.07* (0.5)	-1.2* (0.43)	-0.65 (0.4)	-1.57* (0.47)	1.09* (0.47)	-0.68* (0.34)	-0.71* (0.36)	-0.15 (0.41)	0.44 (0.43)	-0.55 (0.42)	-1.19* (0.46)
19	-1.33* (0.36)	-2.72* (0.39)	-2.55* (0.53)	-1.68* (0.46)	-1.13* (0.44)	-2.05* (0.5)	0.62 (0.5)	-1.16* (0.38)	-1.19* (0.39)	-0.63 (0.44)	-0.04 (0.46)	-1.03* (0.46)	-1.67* (0.49)
20	-0.95* (0.28)	-2.34* (0.31)	-2.17* (0.47)	-1.3* (0.39)	-0.75* (0.36)	-1.67* (0.44)	0.99* (0.44)	-0.78* (0.3)	-0.81* (0.32)	-0.25 (0.37)	0.34 (0.4)	-0.65 (0.39)	-1.29* (0.43)
21	-3.32* (0.39)	-4.71* (0.42)	-4.55* (0.55)	-3.67* (0.48)	-3.12* (0.46)	-4.05* (0.52)	-1.38* (0.52)	-3.16* (0.41)	-3.18* (0.42)	-2.62* (0.47)	-2.04* (0.49)	-3.03* (0.48)	-3.67* (0.51)
22	-1.27* (0.4)	-2.66* (0.43)	-2.49* (0.56)	-1.62* (0.49)	-1.07* (0.47)	-1.99* (0.53)	0.67 (0.53)	-1.1* (0.42)	-1.13* (0.43)	-0.57 (0.47)	0.02 (0.49)	-0.97* (0.49)	-1.61* (0.52)
23	0.03 (0.35)	-1.36* (0.33)	-1.19* (0.48)	-0.31 (0.43)	0.23 (0.43)	-0.69 (0.49)	1.98* (0.45)	0.2 (0.37)	0.17 (0.39)	0.74 (0.43)	1.32* (0.46)	0.33 (0.45)	-0.31 (0.48)
24	0.33 (0.3)	-1.06* (0.28)	-0.89* (0.44)	-0.02 (0.39)	0.53 (0.38)	-0.4 (0.46)	2.27* (0.41)	0.49 (0.32)	0.47 (0.34)	1.03* (0.39)	1.61* (0.42)	0.62 (0.41)	-0.01 (0.45)
T	14	15	16	17	18	19	20	21	22	23	24		
14	—												
15	1.58* (0.22)	—											
16	-0.21 (0.36)	-1.79* (0.31)	—										
17	0.13 (0.36)	-1.45* (0.31)	0.34 (0.38)	—									
18	-0.06 (0.4)	-1.64* (0.36)	0.15 (0.42)	-0.19 (0.42)	—								
19	-0.54 (0.44)	-2.12* (0.4)	-0.33 (0.45)	-0.67 (0.46)	-0.48 (0.48)	—							
20	-0.16 (0.37)	-1.74* (0.32)	0.05 (0.39)	-0.29 (0.39)	-0.1 (0.43)	0.38 (0.46)	—						
21	-2.54* (0.46)	-4.11* (0.43)	-2.32* (0.48)	-2.67* (0.48)	-2.47* (0.51)	-2* (0.54)	-2.37* (0.48)	—					

22	-0.48 (0.47)	-2.06* (0.43)	-0.27 (0.49)	-0.61 (0.49)	-0.42 (0.52)	0.06 (0.54)	-0.32 (0.49)	2.05* (0.56)	—				
23	0.82* (0.38)	-0.76* (0.34)	1.03* (0.44)	0.69 (0.45)	0.88 (0.48)	1.36* (0.51)	0.98* (0.45)	3.36* (0.53)	1.3* (0.54)	—			
24	1.11* (0.34)	-0.46 (0.26)	1.33* (0.41)	0.99* (0.41)	1.18* (0.44)	1.66* (0.47)	1.28* (0.41)	3.65* (0.5)	1.6* (0.51)	0.3 (0.43)	—		

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 13. SRP | 13. SRP + aPDT |
| 14. Control/no treatment | 14. SRP/flap surgery+ Tinidazole + Ampicillin |
| 15. Intensive OHI | 15. SRP + CHX rinse |
| 16. Supragingival cleaning | 16. SRP + AV gel |
| 17. Supragingival cleaning + AZM | 17. SRP + AZM gel |
| 18. Doxy | 18. SRP + ALN gel |
| 19. OHI + SRP | 19. SRP + SMV gel |
| 20. SRP + SDD | 20. SRP + CLM gel |
| 21. SRP + Doxy | 21. SRP + EO-based rinse |
| 22. SRP + AZM | 22. SRP + TET (topical) |
| 23. SRP + MTZ + AMX | 23. SRP + TET (topical) + intensive maintenance |
| 24. SRP + powered subgingival water irrigation | 24. SRP + CHX rinse + Doxy |

TABLE A9.8: BOP---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10
1	—									
2	1.89* (0.17)	—								
3	1.46* (0.2)	-0.42 (0.22)	—							
4	0.42 (0.25)	-1.47* (0.3)	-1.05* (0.32)	—						
5	0.58 (0.34)	-1.3* (0.38)	-0.88* (0.4)	0.17 (0.43)	—					
6	-0.29 (0.27)	-2.18* (0.32)	-1.76* (0.34)	-0.71 (0.37)	-0.88* (0.44)	—				
7	0.06 (0.13)	-1.82* (0.19)	-1.4* (0.22)	-0.35 (0.28)	-0.52 (0.37)	0.36 (0.3)	—			
8	-0.28 (0.16)	-2.17* (0.23)	-1.75* (0.25)	-0.7* (0.3)	-0.87* (0.31)	0.01 (0.31)	-0.35 (0.2)	—		
9	-0.17 (0.26)	-2.05* (0.31)	-1.63* (0.32)	-0.58* (0.26)	-0.75 (0.43)	0.13 (0.37)	-0.23 (0.29)	0.12 (0.3)	—	
10	-1.07* (0.33)	-2.96* (0.37)	-2.54* (0.39)	-1.49* (0.42)	-1.66* (0.48)	-0.78 (0.43)	-1.14* (0.36)	-0.79* (0.37)	-0.91* (0.42)	—
11	0.27 (0.33)	-1.62* (0.37)	-1.19* (0.38)	-0.14 (0.41)	-0.31 (0.45)	0.57 (0.42)	0.21 (0.35)	0.56 (0.33)	0.44 (0.42)	1.34* (0.47)
12	0.51* (0.13)	-1.38* (0.16)	-0.95* (0.2)	0.1 (0.28)	-0.07 (0.37)	0.81* (0.3)	0.45* (0.15)	0.8* (0.21)	0.68* (0.29)	1.58* (0.36)
13	0.62* (0.26)	-1.27* (0.23)	-0.85* (0.29)	0.2 (0.36)	0.03 (0.43)	0.91* (0.37)	0.55* (0.27)	0.9* (0.3)	0.78* (0.36)	1.69* (0.42)
14	-1.59* (0.35)	-3.48* (0.31)	-3.05* (0.38)	-2.01* (0.44)	-2.17* (0.49)	-1.3* (0.45)	-1.65* (0.37)	-1.31* (0.39)	-1.42* (0.44)	-0.52 (0.49)
15	0.44* (0.15)	-1.45* (0.2)	-1.03* (0.23)	0.02 (0.29)	-0.15 (0.37)	0.73* (0.31)	0.37* (0.15)	0.72* (0.21)	0.6* (0.3)	1.51* (0.37)
16	-0.13 (0.39)	-2.02* (0.4)	-1.59* (0.41)	-0.54 (0.46)	-0.71 (0.52)	0.17 (0.47)	-0.19 (0.39)	0.16 (0.42)	0.04 (0.47)	0.94 (0.51)
17	0.3 (0.38)	-1.59* (0.39)	-1.16* (0.4)	-0.12 (0.46)	-0.28 (0.51)	0.59 (0.47)	0.24 (0.39)	0.58 (0.41)	0.47 (0.46)	1.37* (0.51)
18	-0.75* (0.32)	-2.64* (0.33)	-2.22* (0.35)	-1.17* (0.4)	-1.34* (0.47)	-0.46 (0.42)	-0.81* (0.32)	-0.47 (0.35)	-0.59 (0.41)	0.32 (0.46)
19	0.26 (0.53)	-1.63* (0.54)	-1.2* (0.55)	-0.16 (0.59)	-0.32 (0.63)	0.55 (0.6)	0.2 (0.53)	0.54 (0.55)	0.43 (0.59)	1.33* (0.63)

20	-0.29 (0.26)	-2.18* (0.2)	-1.75* (0.29)	-0.71 (0.36)	-0.87* (0.43)	0 (0.38)	-0.35 (0.28)	-0.01 (0.3)	-0.12 (0.37)	0.78 (0.43)
21	-3.33* (0.4)	-5.22* (0.43)	-4.79* (0.44)	-3.74* (0.47)	-3.91* (0.53)	-3.03* (0.48)	-3.39* (0.41)	-3.04* (0.42)	-3.16* (0.47)	-2.26* (0.52)
22	-4.41* (0.61)	-6.3* (0.63)	-5.88* (0.64)	-4.83* (0.66)	-5* (0.7)	-4.12* (0.67)	-4.48* (0.62)	-4.13* (0.63)	-4.25* (0.66)	-3.34* (0.7)
23	-0.78* (0.27)	-2.67* (0.32)	-2.24* (0.34)	-1.19* (0.37)	-1.36* (0.44)	-0.48 (0.38)	-0.84* (0.3)	-0.49 (0.32)	-0.61 (0.37)	0.29 (0.43)
24	-0.36 (0.26)	-2.25* (0.31)	-1.83* (0.32)	-0.78* (0.36)	-0.95* (0.43)	-0.07 (0.37)	-0.43 (0.29)	-0.08 (0.3)	-0.2 (0.36)	0.71 (0.42)
25	-0.66* (0.27)	-2.55* (0.32)	-2.12* (0.34)	-1.08* (0.37)	-1.24* (0.44)	-0.37 (0.38)	-0.72* (0.3)	-0.38 (0.31)	-0.49 (0.37)	0.41 (0.43)
26	-1.36* (0.34)	-3.25* (0.38)	-2.82* (0.39)	-1.77* (0.42)	-1.94* (0.49)	-1.06* (0.44)	-1.42* (0.36)	-1.07* (0.38)	-1.19* (0.43)	-0.29 (0.48)
27	-1.16* (0.4)	-3.05* (0.43)	-2.63* (0.44)	-1.58* (0.47)	-1.75* (0.52)	-0.87 (0.48)	-1.23* (0.42)	-0.88* (0.43)	-1* (0.47)	-0.09 (0.52)
28	0.57 (0.36)	-1.32* (0.32)	-0.9* (0.39)	0.15 (0.44)	-0.02 (0.5)	0.86 (0.45)	0.5 (0.37)	0.85* (0.39)	0.73 (0.45)	1.64* (0.49)
29	1.4* (0.18)	-0.49* (0.09)	-0.07 (0.23)	0.98* (0.31)	0.81* (0.39)	1.69* (0.33)	1.33* (0.21)	1.68* (0.24)	1.56* (0.32)	2.47* (0.38)
T	11	12	13	14	15	16	17	18	19	20
11	—									
12	0.24 (0.35)	—								
13	0.35 (0.41)	0.11 (0.24)	—							
14	-1.86* (0.48)	-2.1* (0.35)	-2.21* (0.38)	—						
15	0.16 (0.36)	-0.08 (0.16)	-0.18 (0.28)	2.02* (0.37)	—					
16	-0.4 (0.51)	-0.64 (0.37)	-0.75 (0.43)	1.46* (0.51)	-0.56 (0.4)	—				
17	0.03 (0.5)	-0.21 (0.35)	-0.32 (0.43)	1.89* (0.5)	-0.13 (0.39)	0.43 (0.51)	—			
18	-1.02* (0.45)	-1.26* (0.29)	-1.37* (0.37)	0.84 (0.45)	-1.19* (0.33)	-0.62 (0.46)	-1.05* (0.46)	—		
19	-0.01 (0.62)	-0.25 (0.51)	-0.36 (0.56)	1.85* (0.62)	-0.18 (0.54)	0.39 (0.36)	-0.04 (0.62)	1.01 (0.59)	—	
20	-0.56 (0.42)	-0.8* (0.25)	-0.91* (0.3)	1.3* (0.37)	-0.73* (0.29)	-0.16 (0.44)	-0.59 (0.44)	0.46 (0.39)	-0.55 (0.57)	—
21	-3.6* (0.51)	-3.84* (0.42)	-3.95* (0.47)	-1.74* (0.53)	-3.76* (0.42)	-3.2* (0.56)	-3.63* (0.55)	-2.58* (0.51)	-3.59* (0.66)	-3.04* (0.47)
22	-4.68* (0.69)	-4.92* (0.62)	-5.03* (0.66)	-2.82* (0.71)	-4.85* (0.63)	-4.28* (0.72)	-4.71* (0.72)	-3.66* (0.69)	-4.67* (0.81)	-4.12* (0.66)
23	-1.05* (0.43)	-1.29* (0.3)	-1.4* (0.38)	0.81 (0.45)	-1.21* (0.31)	-0.65 (0.48)	-1.08* (0.47)	-0.03 (0.42)	-1.04 (0.6)	-0.49 (0.38)
24	-0.64 (0.41)	-0.88* (0.29)	-0.98* (0.36)	1.22* (0.44)	-0.8* (0.3)	-0.24 (0.47)	-0.67 (0.46)	0.39 (0.41)	-0.62 (0.59)	-0.07 (0.36)
25	-0.93* (0.42)	-1.17* (0.3)	-1.28* (0.37)	0.93* (0.45)	-1.1* (0.31)	-0.53 (0.47)	-0.96* (0.47)	0.09 (0.42)	-0.92 (0.6)	-0.37 (0.38)
26	-1.63* (0.47)	-1.87* (0.37)	-1.98* (0.43)	0.23 (0.49)	-1.79* (0.37)	-1.23* (0.52)	-1.66* (0.51)	-0.61 (0.46)	-1.62* (0.63)	-1.07* (0.43)
27	-1.44* (0.51)	-1.68* (0.42)	-1.78* (0.47)	0.43 (0.53)	-1.6* (0.42)	-1.04 (0.56)	-1.46* (0.55)	-0.41 (0.51)	-1.42* (0.66)	-0.87 (0.48)
28	0.3 (0.49)	0.06 (0.36)	-0.05 (0.39)	2.16* (0.45)	0.13 (0.38)	0.7 (0.51)	0.27 (0.5)	1.32* (0.46)	0.31 (0.62)	0.86* (0.38)
29	1.13* (0.37)	0.88* (0.17)	0.78* (0.24)	2.99* (0.33)	0.96* (0.22)	1.52* (0.4)	1.1* (0.39)	2.15* (0.34)	1.14* (0.54)	1.69* (0.22)
T	21	22	23	24	25	26	27	28	29	
21	—									
22	-1.08 (0.73)	—								

23	2.55* (0.48)	3.63* (0.67)	—							
24	2.96* (0.47)	4.05* (0.66)	0.41 (0.38)	—						
25	2.67* (0.48)	3.75* (0.67)	0.12 (0.38)	-0.3 (0.37)	—					
26	1.97* (0.52)	3.05* (0.7)	-0.58 (0.43)	-0.99* (0.43)	-0.7 (0.44)	—				
27	2.16* (0.56)	3.25* (0.73)	-0.39 (0.48)	-0.8 (0.47)	-0.5 (0.48)	0.19 (0.52)	—			
28	3.9* (0.54)	4.98* (0.71)	1.35* (0.45)	0.93* (0.44)	1.23* (0.45)	1.93* (0.5)	1.73* (0.54)	—		
29	4.72* (0.44)	5.81* (0.64)	2.17* (0.33)	1.76* (0.31)	2.06* (0.33)	2.75* (0.39)	2.56* (0.44)	0.83* (0.33)	—	

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 16. SRP | 16. SRP + Doxy+ intensive maintenance |
| 17. Control/no treatment | 17. SRP + AMX+ intensive maintenance |
| 18. Supragingival cleaning | 18. SRP + MTZ + AMX + intensive maintenance |
| 19. Supragingival cleaning + AZM | 19. SRP+ Doxy+ aPDT + intensive maintenance |
| 20. Doxy | 20. SRP/flap surgery+ Tinidazole + Ampicillin |
| 21. SRP + powered subgingival water irrigation | 21. SRP + EO-based rinse |
| 22. SRP + SDD | 22. SRP + SMV gel |
| 23. SRP + Doxy | 23. SRP + CLM gel |
| 24. SRP + AZM | 24. SRP + AV gel |
| 25. SRP + ALN | 25. SRP + AZM gel |
| 26. SRP + aPDT | 26. SRP + ALN gel |
| 27. SRP + intensive maintenance | 27. SRP + TET (topical) |
| 28. SRP + non-intensive maintenance | 28. SRP + TET (topical) + intensive maintenance |
| 29. OHI+ SRP+ intensive maintenance | 29. SRP + CHX rinse + intensive maintenance |
| 30. SRP + SDD + intensive maintenance | |

TABLE A9.9: PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

T**	1	2	3	4	5	6	7	8	9	10	11	12	13
1	—												
2	1.29* (0.13)	—											
3	1.23* (0.38)	-0.05 (0.36)	—										
4	3.85* (0.7)	5.14* (0.68)	5.08* (0.78)	—									
5	0.25 (0.28)	1.04* (0.28)	0.98* (0.46)	4.1* (0.74)	—								
6	0.1 (0.24)	1.18* (0.27)	1.13* (0.45)	3.95* (0.74)	-0.14 (0.37)	—							
7	3.18* (0.45)	1.89* (0.47)	1.94* (0.59)	7.03* (0.83)	2.93* (0.53)	3.07* (0.51)	—						
8	4.17* (0.45)	5.46* (0.43)	5.41* (0.56)	-0.32 (0.81)	4.42* (0.51)	4.28* (0.51)	7.35* (0.64)	—					
9	1.45* (0.31)	2.73* (0.33)	2.68* (0.49)	2.4* (0.76)	-1.7* (0.41)	1.55* (0.39)	4.62* (0.55)	2.73* (0.54)	—				
10	0.05 (0.1)	1.23* (0.16)	1.18* (0.4)	3.9* (0.7)	-0.19 (0.3)	-0.05 (0.26)	3.12* (0.46)	4.23* (0.46)	1.5* (0.32)	—			
11	0.08 (0.15)	1.21* (0.2)	1.15* (0.41)	3.93* (0.71)	-0.17 (0.32)	-0.02 (0.28)	-3.1* (0.43)	4.25* (0.47)	1.53* (0.34)	0.03 (0.18)	—		

12	0.15 (0.24)	- 1.14* (0.27)	- 1.08* (0.45)	4* (0.73)	-0.1 (0.37)	0.05 (0.24)	- 3.02* (0.51)	4.33* (0.51)	1.6* (0.39)	0.1 (0.26)	0.07 (0.28)	—	
13	-0.24 (0.27)	1.53* (0.29)	1.47* (0.46)	3.61* (0.74)	-0.49 (0.38)	-0.34 (0.35)	3.42* (0.52)	3.93* (0.52)	1.21* (0.41)	-0.3 (0.29)	-0.32 (0.3)	-0.39 (0.36)	—
14	-0.01 (0.33)	1.29* (0.35)	1.24* (0.5)	3.85* (0.77)	-0.25 (0.43)	-0.11 (0.4)	3.18* (0.54)	4.17* (0.55)	1.44* (0.45)	-0.06 (0.34)	-0.09 (0.33)	-0.16 (0.4)	0.24 (0.42)
15	-0.6* (0.23)	1.89* (0.19)	1.84* (0.41)	3.25* (0.71)	- 0.85* (0.34)	- 0.71* (0.33)	3.78* (0.5)	3.57* (0.47)	0.84* (0.38)	- 0.66* (0.25)	- 0.68* (0.27)	- 0.76* (0.33)	-0.36 (0.35)
16	0.66* (0.15)	0.63* (0.09)	-0.58 (0.35)	4.51* (0.69)	0.41 (0.29)	0.55* (0.28)	2.52* (0.48)	4.83* (0.44)	2.1* (0.34)	0.6* (0.18)	0.58* (0.21)	0.5 (0.28)	0.9* (0.3)
17	0.44 (0.27)	0.85* (0.29)	-0.79 (0.47)	4.29* (0.74)	0.19 (0.38)	0.33 (0.35)	2.74* (0.53)	4.61* (0.52)	1.89* (0.4)	0.38 (0.29)	0.36 (0.31)	0.29 (0.36)	0.68 (0.38)
18	- 1.05* (0.27)	2.33* (0.3)	2.28* (0.47)	2.8* (0.75)	- 1.29* (0.39)	- 1.15* (0.36)	- 4.22* (0.53)	3.13* (0.53)	0.4 (0.41)	-1.1* (0.29)	- 1.13* (0.31)	-1.2* (0.36)	-0.8* (0.38)
19	-0.29 (0.26)	1.58* (0.29)	1.52* (0.46)	3.56* (0.74)	-0.54 (0.38)	-0.39 (0.36)	3.47* (0.52)	3.88* (0.52)	1.16* (0.41)	-0.34 (0.28)	-0.37 (0.31)	-0.44 (0.36)	-0.05 (0.38)
20	-0.29 (0.31)	1.58* (0.33)	1.53* (0.49)	3.56* (0.76)	-0.54 (0.41)	-0.4 (0.39)	3.47* (0.55)	3.88* (0.54)	1.15* (0.44)	-0.35 (0.33)	-0.37 (0.34)	-0.45 (0.39)	-0.05 (0.41)
21	-0.59 (0.34)	1.88* (0.36)	1.82* (0.51)	3.26* (0.77)	-0.84 (0.43)	-0.69 (0.41)	3.77* (0.56)	3.58* (0.56)	0.86 (0.46)	-0.64 (0.35)	-0.67 (0.37)	-0.74 (0.41)	-0.35 (0.43)
22	-0.26 (0.27)	1.55* (0.3)	1.49* (0.47)	3.59* (0.75)	-0.51 (0.38)	-0.36 (0.36)	3.44* (0.52)	3.91* (0.52)	1.19* (0.4)	-0.31 (0.29)	-0.34 (0.31)	-0.41 (0.36)	-0.02 (0.37)
23	- 5.16* (0.53)	6.44* (0.54)	6.39* (0.65)	-1.3 (0.88)	-5.4* (0.6)	- 5.26* (0.58)	- 8.33* (0.7)	-0.98 (0.69)	- 3.71* (0.61)	- 5.21* (0.54)	- 5.24* (0.55)	- 5.31* (0.58)	- 4.91* (0.59)
24	-0.27 (0.23)	1.55* (0.26)	-1.5* (0.45)	3.58* (0.73)	-0.51 (0.36)	-0.37 (0.33)	3.44* (0.5)	3.91* (0.5)	1.18* (0.38)	-0.32 (0.25)	-0.35 (0.27)	-0.42 (0.33)	-0.02 (0.35)
25	0.44 (0.29)	0.85* (0.27)	-0.79 (0.44)	4.29* (0.73)	0.19 (0.39)	0.34 (0.38)	2.74* (0.54)	4.61* (0.51)	1.89* (0.43)	0.38 (0.31)	0.36 (0.33)	0.29 (0.38)	0.68 (0.4)
T	14	15	16	17	18	19	20	21	22	23	24	25	
14	—												
15	-0.6 (0.4)	—											
16	0.66 (0.36)	1.26* (0.21)	—										
17	0.44 (0.42)	1.04* (0.35)	-0.22 (0.3)	—									
18	- 1.04* (0.43)	-0.44 (0.36)	-1.7* (0.31)	- 1.48* (0.38)	—								
19	-0.29 (0.42)	0.31 (0.35)	0.95* (0.3)	-0.73 (0.38)	0.76* (0.38)	—							
20	-0.29 (0.45)	0.31 (0.38)	0.95* (0.34)	-0.73 (0.41)	0.75 (0.41)	0 (0.41)	—						
21	-0.58 (0.47)	0.01 (0.41)	1.25* (0.37)	- 1.03* (0.43)	0.46 (0.43)	-0.3 (0.43)	-0.3 (0.46)	—					
22	-0.26 (0.42)	0.34 (0.35)	- 0.92*	-0.7 (0.37)	0.79* (0.38)	0.03 (0.37)	0.03 (0.41)	0.33 (0.43)	—				

			(0.31)										
23	- 5.15* (0.62)	- 4.55* (0.58)	- 5.81* (0.55)	- 5.59* (0.59)	- 4.11* (0.59)	- 4.86* (0.59)	- 4.86* (0.61)	- 4.57* (0.63)	- 4.89* (0.59)	—			
24	-0.26 (0.4)	0.34 (0.32)	- 0.92* (0.27)	-0.7* (0.35)	0.78* (0.35)	0.02 (0.35)	0.03 (0.38)	0.32 (0.41)	-0.01 (0.35)	4.89* (0.57)	—		
25	0.44 (0.44)	1.04* (0.33)	-0.22 (0.25)	0 (0.4)	1.49* (0.4)	0.73 (0.4)	0.73 (0.43)	1.03* (0.45)	0.7 (0.4)	5.59* (0.6)	0.7 (0.37)	—	

T: treatment

* Statistically significant

**Legend:

- | | |
|--|---|
| 10. SRP | 14. SRP + aPDT |
| 11. Control/no treatment | 15. SRP/flap surgery+ Tinidazole + Ampicillin |
| 12. Intensive OHI | 16. SRP + CHX rinse |
| 13. CHX rinse | 17. SRP + SZ gel |
| 14. Supragingival cleaning | 18. SRP + AV gel |
| 15. Supragingival cleaning + AZM | 19. SRP + AZM gel |
| 16. Doxy | 20. SRP + ALN gel |
| 17. OHI + SRP | 21. SRP + SMV gel |
| 18. SRP + powered subgingival water irrigation | 22. SRP + CLM gel |
| 19. SRP + SDD | 23. SRP + EO-based rinse |
| 20. SRP + Doxy | 24. SRP + TET (topical) |
| 21. SRP + AZM | 25. SRP + CHX rinse + Doxy |
| 22. SRP + MTZ + AMX | |

**TABLE A9.10: PI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY
(MEAN±SD)**

T**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	1.7* (0.15)	—									
3	-5.49* (0.97)	-7.18* (0.96)	—								
4	-3.88* (0.7)	-5.58* (0.68)	1.61 (1.14)	—							
5	0.43 (0.24)	-1.26* (0.25)	5.92* (0.99)	4.31* (0.73)	—						
6	0.25 (0.25)	-1.45* (0.29)	5.73* (1)	4.13* (0.74)	-0.19 (0.34)	—					
7	3.25* (0.46)	1.55* (0.48)	8.74* (1.08)	7.13* (0.83)	2.82* (0.51)	3.01* (0.52)	—				
8	-1.45* (0.31)	-3.14* (0.34)	4.04* (1.02)	2.43* (0.76)	-1.88* (0.39)	-1.69* (0.4)	-4.7* (0.55)	—			
9	0.27* (0.13)	-1.43* (0.18)	5.75* (0.98)	4.15* (0.7)	-0.17 (0.27)	0.02 (0.29)	-2.99* (0.48)	1.71* (0.33)	—		
10	0.16 (0.15)	-1.54* (0.21)	5.64* (0.98)	4.04* (0.71)	-0.28 (0.28)	-0.09 (0.3)	-3.1* (0.43)	1.6* (0.34)	-0.11 (0.2)	—	
11	0.42 (0.26)	-1.28* (0.3)	5.91* (1)	4.3* (0.74)	-0.02 (0.35)	0.17 (0.26)	-2.83* (0.53)	1.86* (0.4)	0.15 (0.29)	0.26 (0.3)	—
12	0.03 (0.33)	-1.67* (0.36)	5.52* (1.03)	3.91* (0.77)	-0.4 (0.4)	-0.22 (0.41)	-3.22* (0.54)	1.48* (0.45)	-0.24 (0.35)	-0.13 (0.33)	-0.39 (0.42)
13	0.48* (0.13)	-1.22* (0.15)	5.97* (0.97)	4.36* (0.7)	0.05 (0.26)	0.24 (0.28)	-2.77* (0.48)	1.93* (0.33)	0.22 (0.15)	0.33 (0.2)	0.06 (0.29)
14	1.06* (0.23)	-0.64* (0.2)	6.55* (0.98)	4.94* (0.71)	0.62* (0.31)	0.81* (0.34)	-2.19* (0.51)	2.5* (0.38)	0.79* (0.24)	0.9* (0.27)	0.64 (0.35)
15	-4.45* (0.5)	-6.15* (0.47)	1.04 (1.07)	-0.57 (0.83)	-4.88* (0.54)	-4.69* (0.56)	-7.7* (0.68)	-3* (0.58)	-4.71* (0.51)	-4.6* (0.52)	-4.87* (0.56)
16	0.46* (0.15)	-1.23* (0.19)	5.95* (0.98)	4.34* (0.71)	0.03 (0.27)	0.22 (0.29)	-2.79* (0.48)	1.91* (0.34)	0.2 (0.15)	0.31 (0.21)	0.05 (0.3)
17	0.34 (0.38)	-1.36* (0.39)	5.83* (1.05)	4.22* (0.78)	-0.09 (0.44)	0.09 (0.46)	-2.91* (0.6)	1.79* (0.49)	0.07 (0.39)	0.18 (0.41)	-0.08 (0.46)

18	0.62 (0.38)	-1.08* (0.39)	6.1* (1.04)	4.5* (0.78)	0.18 (0.44)	0.37 (0.46)	-2.64* (0.6)	2.06* (0.49)	0.35 (0.39)	0.46 (0.41)	0.2 (0.46)
19	0.33 (0.3)	-1.37* (0.3)	5.81* (1.01)	4.21* (0.75)	-0.11 (0.37)	0.08 (0.39)	-2.93* (0.54)	1.77* (0.43)	0.06 (0.3)	0.17 (0.33)	-0.09 (0.4)
20	1.32* (0.54)	-0.37 (0.54)	6.81* (1.12)	5.2* (0.87)	0.89 (0.58)	1.08 (0.6)	-1.93* (0.71)	2.77* (0.62)	1.06* (0.55)	1.17* (0.56)	0.91 (0.6)
21	-0.19 (0.24)	-1.89* (0.19)	5.29* (0.98)	3.68* (0.71)	-0.63* (0.32)	-0.44 (0.35)	-3.45* (0.51)	1.25* (0.39)	-0.46 (0.26)	-0.35 (0.28)	-0.61 (0.36)
22	-6.07* (0.9)	-7.76* (0.35)	-0.58 (0.35)	-2.19* (1.08)	-6.5* (0.93)	-6.31* (0.94)	-9.32* (1.01)	-4.62* (0.96)	-6.33* (0.91)	-6.22* (0.92)	-6.48* (0.94)
23	-5.15* (0.53)	-6.85* (0.55)	0.34 (1.11)	-1.27 (0.87)	-5.59* (0.58)	-5.4* (0.58)	-8.4* (0.69)	-3.71* (0.61)	-5.42* (0.54)	-5.31* (0.55)	-5.57* (0.59)
24	-0.3 (0.33)	-2* (0.36)	5.18* (1.02)	3.58* (0.77)	-0.74 (0.41)	-0.55 (0.42)	-3.56* (0.57)	1.14* (0.45)	-0.57 (0.36)	-0.46 (0.37)	-0.72 (0.42)
25	-0.81* (0.27)	-2.51* (0.31)	4.67* (1.01)	3.06* (0.75)	-1.25* (0.36)	-1.06* (0.37)	-4.07* (0.53)	0.63 (0.41)	-1.08* (0.3)	-0.97* (0.31)	-1.23* (0.38)
26	0.68* (0.27)	-1.02* (0.31)	6.17* (1.01)	4.56* (0.75)	0.24 (0.36)	0.43 (0.37)	-2.57* (0.53)	2.12* (0.41)	0.41 (0.3)	0.52 (0.31)	0.26 (0.37)
27	-0.14 (0.26)	-1.84* (0.3)	5.34* (1)	3.74* (0.74)	-0.58 (0.35)	-0.39 (0.36)	-3.4* (0.52)	1.3* (0.4)	-0.41 (0.29)	-0.3 (0.3)	-0.56 (0.36)
28	-0.78* (0.27)	-2.48* (0.31)	4.71* (1.01)	3.1* (0.75)	-1.22* (0.36)	-1.03* (0.37)	-4.03* (0.53)	0.67 (0.41)	-1.05* (0.3)	-0.94* (0.31)	-1.2* (0.38)
29	-0.13 (0.31)	-1.82* (0.34)	5.36* (1.02)	3.75* (0.76)	-0.56 (0.39)	-0.37 (0.4)	-3.38* (0.55)	1.32* (0.43)	-0.39 (0.33)	-0.28 (0.34)	-0.54 (0.4)
30	0.19 (0.27)	-1.5* (0.3)	5.68* (1)	4.07* (0.74)	-0.24 (0.35)	-0.05 (0.37)	-3.06* (0.53)	1.64* (0.4)	-0.07 (0.3)	0.04 (0.31)	-0.22 (0.37)
31	1.83* (0.5)	0.13 (0.49)	7.32* (1.08)	5.71* (0.84)	1.39* (0.54)	1.58* (0.56)	-1.42* (0.68)	3.27* (0.58)	1.56* (0.51)	1.67* (0.52)	1.41* (0.56)
32	1.21* (0.17)	-0.49* (0.09)	6.7* (0.97)	5.09* (0.68)	0.78* (0.27)	0.97* (0.3)	-2.04* (0.48)	2.66* (0.35)	0.95* (0.2)	1.06* (0.22)	0.79* (0.31)
33	-6.28* (0.94)	-7.98* (0.93)	-0.79 (0.44)	-2.4* (1.11)	-6.71* (0.96)	-6.53* (0.97)	-9.53* (1.04)	-4.83* (0.99)	-6.55* (0.94)	-6.44* (0.95)	-6.7* (0.97)
T	12	13	14	15	16	17	18	19	20	21	22
12	—										
13	0.45 (0.35)	—									
14	1.03* (0.4)	0.58* (0.21)	—								
15	-4.48* (0.6)	-4.93* (0.5)	-5.51* (0.52)	—							
16	0.43 (0.36)	-0.02 (0.16)	-0.59* (0.25)	4.91* (0.51)	—						
17	0.31 (0.5)	-0.14 (0.36)	-0.72 (0.42)	4.79* (0.61)	-0.12 (0.39)	—					
18	0.59 (0.5)	0.13 (0.36)	-0.44 (0.41)	5.06* (0.61)	0.15 (0.39)	0.28 (0.5)	—				
19	0.3 (0.44)	-0.16 (0.26)	-0.73* (0.34)	4.77* (0.56)	-0.14 (0.31)	-0.01 (0.45)	-0.29 (0.44)	—			
20	1.29* (0.63)	0.84 (0.53)	0.27 (0.56)	5.77* (0.72)	0.86 (0.55)	0.98* (0.38)	0.71 (0.63)	1 (0.59)	—		
21	-0.22 (0.41)	-0.68* (0.24)	-1.25* (0.28)	4.25* (0.51)	-0.66* (0.27)	-0.53 (0.43)	-0.81 (0.43)	-0.52 (0.36)	-1.52* (0.58)	—	
22	-6.1* (0.96)	-6.55* (0.91)	-7.12* (0.92)	-1.62 (1.01)	-6.53* (0.91)	-6.4* (0.98)	-6.68* (0.97)	-6.39* (0.94)	-7.39* (1.06)	-5.87* (0.91)	—
23	-5.18* (0.62)	-5.63* (0.54)	-6.21* (0.57)	-0.7 (0.72)	-5.62* (0.55)	-5.49* (0.65)	-5.77* (0.65)	-5.48* (0.6)	-6.48* (0.75)	-4.96* (0.58)	0.91 (1.05)
24	-0.33 (0.47)	-0.79* (0.36)	-1.36* (0.4)	4.14* (0.6)	-0.77* (0.36)	-0.64 (0.51)	-0.92 (0.51)	-0.63 (0.44)	-1.63* (0.64)	-0.11 (0.41)	5.76* (0.96)
25	-0.84* (0.43)	-1.3* (0.3)	-1.87* (0.36)	3.63* (0.57)	-1.28* (0.31)	-1.15* (0.47)	-1.43* (0.47)	-1.14* (0.4)	-2.14* (0.61)	-0.62 (0.37)	5.25* (0.94)
26	0.65 (0.42)	0.2 (0.3)	-0.38 (0.35)	5.13* (0.57)	0.21 (0.31)	0.34 (0.47)	0.06 (0.47)	0.35 (0.4)	-0.65 (0.61)	0.87* (0.36)	6.74* (0.94)
27	-0.17 (0.42)	-0.63* (0.29)	-1.2* (0.35)	4.3* (0.56)	-0.61* (0.3)	-0.48 (0.46)	-0.76 (0.46)	-0.47 (0.39)	-1.47* (0.6)	0.05 (0.35)	5.92* (0.94)

28	-0.81 (0.43)	-1.26* (0.3)	-1.84* (0.36)	3.67* (0.57)	-1.25* (0.31)	-1.12* (0.47)	-1.4* (0.47)	-1.11* (0.41)	-2.11* (0.61)	-0.59 (0.37)	5.28* (0.94)
29	-0.16 (0.45)	-0.61 (0.33)	-1.18* (0.38)	4.32* (0.58)	-0.59 (0.34)	-0.47 (0.49)	-0.74 (0.49)	-0.45 (0.43)	-1.45* (0.62)	0.07 (0.39)	5.94* (0.95)
30	0.16 (0.42)	-0.29 (0.3)	-0.86* (0.35)	4.64* (0.56)	-0.27 (0.3)	-0.15 (0.46)	-0.42 (0.47)	-0.13 (0.4)	-1.13 (0.6)	0.39 (0.36)	6.26* (0.94)
31	1.8* (0.59)	1.35* (0.49)	0.77 (0.44)	6.28* (0.68)	1.36* (0.51)	1.49* (0.61)	1.21* (0.61)	1.5* (0.56)	0.5 (0.72)	2.02* (0.52)	7.89* (1.01)
32	1.18* (0.37)	0.73* (0.16)	0.15 (0.22)	5.66* (0.48)	0.75* (0.2)	0.87* (0.4)	0.6 (0.39)	0.89* (0.31)	-0.11 (0.55)	1.41* (0.21)	7.28* (0.9)
33	-6.31* (0.99)	-6.76* (0.94)	-7.34* (0.95)	-1.83 (1.04)	-6.74* (0.95)	-6.62* (1.02)	-6.9* (1.01)	-6.61* (0.98)	-7.6* (1.09)	-6.08* (0.95)	-0.21 (0.26)
T	23	24	25	26	27	28	29	30	31	32	33
23	—										
24	4.85* (0.62)	—									
25	4.34* (0.59)	-0.51 (0.43)	—								
26	5.83* (0.59)	0.98* (0.43)	1.49* (0.38)	—							
27	5.01* (0.59)	0.16 (0.42)	0.67 (0.38)	-0.82* (0.37)	—						
28	4.37* (0.59)	-0.48 (0.43)	0.03 (0.39)	-1.46* (0.38)	-0.64 (0.38)	—					
29	5.03* (0.61)	0.18 (0.45)	0.69 (0.41)	-0.8* (0.41)	0.02 (0.4)	0.66 (0.41)	—				
30	5.35* (0.59)	0.5 (0.43)	1.01* (0.38)	-0.48 (0.38)	0.34 (0.37)	0.97* (0.38)	0.32 (0.41)	—			
31	6.98* (0.72)	2.13* (0.6)	2.64* (0.57)	1.15* (0.57)	1.97* (0.56)	2.61* (0.57)	1.95* (0.59)	1.63* (0.57)	—		
32	6.36* (0.55)	1.52* (0.37)	2.03* (0.32)	0.53 (0.32)	1.36* (0.31)	1.99* (0.32)	1.34* (0.35)	1.02* (0.31)	-0.62 (0.49)	—	
33	-1.13 (1.08)	-5.98* (0.99)	-5.46* (0.97)	-6.96* (0.98)	-6.14* (0.97)	-5.5* (0.98)	-6.15* (0.99)	-6.47* (0.97)	-8.11* (1.05)	-7.49* (0.94)	—

T: treatment

* Statistically significant

**Legend:

- | | | |
|--|---|---|
| 23. SRP | 12. SRP + aPDT | 23. SRP + EO-based rinse |
| 24. Control/no treatment | 13. SRP + intensive maintenance | 24. SRP + SMV gel |
| 25. Intensive OHI | 14. SRP + non-intensive maintenance | 25. SRP + CLM gel |
| 26. CHX rinse | 15. OHI+ SRP+ intensive maintenance | 26. SRP + SZ gel |
| 27. Supragingival cleaning | 16. SRP + SDD + intensive maintenance | 27. SRP + AV gel |
| 28. Supragingival cleaning + AZM | 17. SRP + Doxy+ intensive maintenance | 28. SRP + AZM gel |
| 29. Doxy | 18. SRP + AMX+ intensive maintenance | 29. SRP + ALN gel |
| 30. SRP + powered subgingival water irrigation | 19. SRP + MTZ + AMX + intensive maintenance | 30. SRP + TET (topical) |
| 31. SRP + SDD | 20. SRP+ Doxy+ aPDT + intensive maintenance | 31. SRP + TET (topical) + non-intensive maintenance |
| 32. SRP + Doxy | 21. SRP/flap surgery+ Tinidazole + Ampicillin | 32. SRP + CHX rinse + intensive maintenance |
| 33. SRP + AZM | 22. SRP + CHX rinse | 33. SRP + CHX rinse + Doxy |

TABLE A9.11: GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT 3 MONTHS

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	2.9* (0.32)	—										
3	-1.18* (0.47)	-4.08* (0.34)	—									
4	0.11 (0.11)	-2.79* (0.34)	1.29* (0.48)	—								
5	0.17	-2.73*	1.35*	0.06	—							

	(0.16)	(0.35)	(0.49)	(0.19)								
6	-2.87* (0.44)	-5.77* (0.55)	-1.69* (0.64)	-2.98* (0.45)	-3.05* (0.47)	—						
7	-0.65* (0.28)	-3.55* (0.43)	0.53 (0.55)	-0.76* (0.3)	-0.83* (0.32)	2.22* (0.52)	—					
8	1.65* (0.45)	-1.25* (0.32)	2.83* (0.47)	1.54* (0.47)	1.48* (0.47)	4.53* (0.63)	2.31* (0.53)	—				
9	2.47* (0.34)	-0.43* (0.09)	3.65* (0.35)	2.36* (0.35)	2.29* (0.36)	5.34* (0.55)	3.12* (0.44)	0.82* (0.32)	—			
10	-2.34* (0.34)	-5.24* (0.47)	-1.16* (0.58)	-2.45* (0.36)	-2.51* (0.37)	0.54 (0.55)	-1.68* (0.44)	-3.99* (0.56)	-4.8* (0.48)	—		
11	-0.52 (0.27)	-3.42* (0.42)	0.66 (0.54)	-0.63* (0.29)	-0.69* (0.32)	2.35* (0.52)	0.13 (0.39)	-2.17* (0.53)	-2.99* (0.43)	1.82* (0.43)	—	
12	0.5 (0.36)	-2.4* (0.48)	1.68* (0.59)	0.39 (0.38)	0.33 (0.39)	3.38* (0.57)	1.16* (0.46)	-1.15* (0.58)	-1.96* (0.49)	2.84* (0.49)	1.02* (0.45)	—

T: treatment

* Statistically significant

**Legend:

- | | |
|-----------------------------|---|
| 5. SRP | 7. SRP + powered subgingival water irrigation |
| 6. Control/no treatment | 8. CHX rinse |
| 7. OHI + SRP | 9. SRP + CHX rinse |
| 8. SRP + SDD | 10. SRP + SZ gel |
| 9. SRP + Doxy | 11. SRP + CLM gel |
| 10. SRP + Omega 3 + aspirin | 12. SRP + TET (topical) |

TABLE A9.12: GI ---- HEAD-TO-HEAD COMPARISON OF PERIODONTAL THERAPY AT END OF STUDY

(MEAN±SD)

T**	1	2	3	4	5	6	7	8	9	10	11
1	—										
2	2.89* (0.34)	—									
3	1.39* (0.49)	-1.5* (0.35)	—								
4	1.74* (0.32)	-1.15* (0.47)	0.36 (0.59)	—							
5	-0.66* (0.28)	-3.54* (0.44)	-2.04* (0.56)	-2.4* (0.43)	—						
6	1.92* (0.47)	-0.97* (0.33)	0.53 (0.36)	0.17 (0.57)	2.57* (0.55)	—					
7	0.4* (0.15)	-2.49* (0.37)	-0.99 (0.51)	-1.35* (0.32)	1.05* (0.32)	-1.52* (0.49)	—				
8	0.16 (0.16)	-2.73* (0.36)	-1.22* (0.51)	-1.58* (0.36)	0.82* (0.33)	-1.75* (0.49)	-0.23 (0.22)	—			
9	-2.32* (0.4)	-5.21* (0.53)	-3.71* (0.63)	-4.07* (0.52)	-1.67* (0.49)	-4.24* (0.62)	-2.72* (0.43)	-2.49* (0.43)	—		
10	0.29 (0.15)	-2.6* (0.37)	-1.1* (0.51)	-1.45* (0.29)	0.95* (0.32)	-1.63* (0.5)	-0.11 (0.15)	0.13 (0.22)	2.61* (0.43)	—	
11	-1.19* (0.48)	-4.08* (0.35)	-2.58* (0.49)	-2.94* (0.58)	-0.54 (0.56)	-3.11* (0.48)	-1.59* (0.51)	-1.36* (0.5)	1.13 (0.63)	-1.48* (0.51)	—
12	2.5* (0.35)	-0.39* (0.09)	1.12* (0.36)	0.76 (0.48)	3.16* (0.45)	0.59 (0.34)	2.11* (0.38)	2.34* (0.38)	4.82* (0.53)	2.21* (0.38)	3.69* (0.36)
13	0.49* (0.15)	-2.4* (0.37)	-0.89 (0.51)	-1.25* (0.33)	1.15* (0.32)	-1.43* (0.5)	0.1 (0.15)	0.33 (0.22)	2.81* (0.43)	0.2 (0.16)	1.68* (0.51)
14	-2.57* (0.35)	-5.46* (0.49)	-3.95* (0.6)	-4.31* (0.48)	-1.91* (0.45)	-4.48* (0.59)	-2.96* (0.38)	-2.73* (0.39)	-0.24 (0.54)	-2.86* (0.38)	-1.37* (0.6)
15	-1.26* (0.29)	-4.14* (0.45)	-2.64* (0.57)	-3* (0.43)	-0.6 (0.4)	-3.17* (0.55)	-1.65* (0.32)	-1.42* (0.33)	1.07* (0.49)	-1.55* (0.33)	-0.06 (0.56)
16	0.51 (0.36)	-2.38* (0.5)	-0.87 (0.6)	-1.23* (0.49)	1.17* (0.46)	-1.41* (0.59)	0.12 (0.39)	0.35 (0.4)	2.83* (0.54)	0.22 (0.39)	1.7* (0.6)
T	12	13	14	15	16						

12	—										
13	-2.01* (0.38)	—									
14	-5.07* (0.5)	-3.06* (0.39)	—								
15	-3.76* (0.46)	-1.75* (0.33)	1.31* (0.46)	—							
16	-1.99* (0.5)	0.02 (0.39)	3.08* (0.5)	1.77* (0.46)	—						

T: treatment

* Statistically significant

** Legend:

- | | |
|--|---|
| 7. SRP | 9. SRP + Omega 3 + aspirin |
| 8. Control/no treatment | 10. SRP + intensive maintenance |
| 9. CHX rinse | 11. OHI+ SRP+ intensive maintenance |
| 10. Supragingival cleaning | 12. SRP + CHX rinse + intensive maintenance |
| 11. SRP + powered subgingival water irrigation | 13. SRP + SDD + intensive maintenance |
| 12. SRP + CHX rinse | 14. SRP + SZ gel |
| 13. SRP + SDD | 15. SRP + CLM gel |
| 14. SRP + Doxy | 16. SRP + TET (topical) |

TABLE A9.13: TOTAL WITHDRAWALS (RELATIVE RISK ± 95% CREDIBLE INTERVAL)

T**	1	2	3	4	5	6	7	8	9	10	11	12
1	—											
2	1.74 (0.92,3.19)	—										
3	0.51 (0.11,76)	0.29 (0.6,77)	—									
4	0.98 (0.23,3.43)	0.57 (0.14,1.84)	1.91 (0.06,219.7)	—								
5	0.65 (0.16,2.33)	0.37 (0.08,1.53)	1.26 (0.04,146.1)	0.66 (0.1,4.49)	—							
6	3.08 (0.84,9.56)	1.76 (0.43,6.4)	5.98 (0.2,713.7)	3.12 (0.53,19.41)	4.71 (0.76,29.54)	—						
7	0.99 (0.4,2.37)	0.57 (0.19,1.67)	1.93 (0.07,215.5)	1.01 (0.22,5.53)	1.53 (0.32,8.14)	0.33 (0.09,1.21)	—					
8	0.91 (0.25,2.94)	0.52 (0.12,1.98)	1.77 (0.06,204.9)	0.93 (0.15,5.97)	1.38 (0.35,6.01)	0.3 (0.05,1.73)	0.92 (0.19,4.12)	—				
9	1.64 (0.49,4.83)	0.94 (0.32,2.52)	3.13 (0.12,359.1)	1.65 (0.51,6.08)	2.52 (0.44,15.35)	0.53 (0.1,2.81)	1.65 (0.38,6.66)	1.8 (0.33,9.74)	—			
10	1.03	0.59	1.93	1.05	1.56	0.33	1.04	1.12	0.64	—		

	(0.14,4.8 3)	(0.09,2.53)	(0.05,253)	(0.13,6.64)	(0.15,13.1 4)	(0.03,2.58)	(0.12,6.35)	(0.11,8.71)	(0.09,2.87)			
11	2.09 (0.49,7.1 7)	1.2 (0.32,3.73)	4.04 (0.13,466. 9)	2.12 (0.36,12.5)	3.21 (0.47,21.1 3)	0.69 (0.11,3.97)	2.1 (0.39,9.57)	2.3 (0.36,14.0 9)	1.28 (0.25,6.21)	2.05 (0.28,18.4 1)	—	
12	0.44 (0.05,2.9 3)	0.25 (0.03,1.58)	0.86 (0.02,122)	0.46 (0.05,3.31)	0.68 (0.05,7.27)	0.14 (0.01,1.39)	0.45 (0.04,3.6)	0.49 (0.04,4.84)	0.28 (0.04,1.22)	0.43 (0.04,4.92)	0.21 (0.02,2.01)	—
13	0.79 (0.03,8.8 9)	0.46 (0.02,5.63)	1.55 (0.02,272. 6)	0.81 (0.03,13.2 1)	1.23 (0.04,20.7 5)	0.26 (0.01,3.91)	0.81 (0.03,10.3 6)	0.87 (0.03,13.6 6)	0.49 (0.02,7.16)	0.78 (0.02,17.4 4)	0.38 (0.01,6.38)	1.8 (0.05,48.2 8)
14	1.13 (0.12,6.5 4)	0.64 (0.06,4.21)	2.18 (0.04,298. 4)	1.14 (0.09,11.1 4)	1.73 (0.13,16.5 9)	0.36 (0.03,3.06)	1.13 (0.11,7.33)	1.24 (0.1,11.26)	0.69 (0.06,5.7)	1.11 (0.07,15.3 2)	0.53 (0.04,5.22)	2.54 (0.14,42.4 5)
15	0.83 (0.14,44)	0.48 (0.8,45)	1.48 (0.268,4)	0.85 (0.21,4)	1.25 (0.33,05)	0.27 (0.6,41)	0.83 (0.17,24)	0.9 (0.22,37)	0.51 (0.11,34)	0.81 (0.28,17)	0.4 (0.10,04)	1.86 (0.01,77.3 4)
16	0.97 (0.01,13. 58)	0.55 (0.01,8.05)	1.71 (0.44,9.21)	0.99 (0.01,20.0 1)	1.49 (0.01,31.4 5)	0.32 (0.6,21)	0.98 (0.01,16.1 2)	1.05 (0.01,21.3 8)	0.6 (0.01,10.2 8)	0.96 (0.01,26.1 6)	0.47 (0.9,55)	2.2 (0.02,72.7 5)
17	1.33 (0.28,5.5 5)	0.76 (0.15,3.65)	2.58 (0.08,345. 3)	1.38 (0.18,10.3 1)	2.04 (0.28,15.3 8)	0.44 (0.06,2.97)	1.35 (0.23,7.35)	1.47 (0.21,10.2 7)	0.82 (0.12,5.32)	1.33 (0.14,14.7 8)	0.64 (0.08,4.81)	3.01 (0.26,44.3 8)
18	0.64 (0.01,12. 78)	0.36 (0.7,69)	1.18 (0.301,6)	0.65 (0.01,18.1 8)	0.97 (0.01,27.0 5)	0.21 (0.5,21)	0.65 (0.01,14.0 3)	0.7 (0.01,18.7 6)	0.39 (0.9,94)	0.62 (0.01,22.8 2)	0.31 (0.8,52)	1.41 (0.01,62.8 3)
19	1.36 (0.29,5.7 5)	0.78 (0.15,3.7)	2.68 (0.08,330. 8)	1.4 (0.19,10.6 6)	2.1 (0.29,15.9 8)	0.44 (0.07,3.06)	1.38 (0.24,7.57)	1.51 (0.22,10.4 5)	0.84 (0.12,5.54)	1.35 (0.15,14.9 2)	0.65 (0.09,5.01)	3.12 (0.26,44.8 5)
20	0.86 (0.03,9.7 2)	0.5 (0.02,6.08)	1.63 (0.02,311. 9)	0.89 (0.03,14.3 5)	1.34 (0.04,21.9 7)	0.29 (0.01,4.17)	0.87 (0.03,11.4)	0.96 (0.03,15.0 1)	0.53 (0.02,7.87)	0.85 (0.02,19.1 7)	0.42 (0.01,6.84)	1.96 (0.05,55.7 9)
21	1.83 (0.17,13. 08)	1.05 (0.09,8.2)	3.49 (0.07,545. 7)	1.87 (0.13,21.7 4)	2.82 (0.19,31.6 9)	0.6 (0.04,6.01)	1.85 (0.15,15.6 4)	2.03 (0.15,20.8 2)	1.13 (0.08,11.2 4)	1.82 (0.11,28.6 5)	0.89 (0.06,10.4 2)	4.16 (0.21,82.6 6)
22	0.68 (0.13,2.9 3)	0.39 (0.07,1.94)	1.33 (0.04,164. 1)	0.7 (0.09,5.44)	1.05 (0.13,7.88)	0.22 (0.03,1.56)	0.69 (0.11,3.88)	0.75 (0.1,5.31)	0.42 (0.06,2.78)	0.67 (0.07,7.91)	0.33 (0.04,2.52)	1.53 (0.13,23.3 2)
23	0.66 (0.01,13. 69)	0.38 (0.7,79)	1.26 (0,339,8)	0.7 (0.01,18.0 6)	1.02 (0.01,29.6 7)	0.22 (0,5,93)	0.67 (0.01,16.2 4)	0.74 (0,20,65)	0.41 (0,9,47)	0.69 (0.01,14.0 2)	0.32 (0,9,08)	1.53 (0.01,61.4 1)
24	1.35	0.77	2.64	1.38	2.08	0.44	1.36	1.49	0.83	1.3	0.65	3.03

	(0.56,3.12)	(0.42,1.38)	(0.11,271.5)	(0.37,5.93)	(0.44,10.77)	(0.11,2.01)	(0.39,4.71)	(0.34,6.99)	(0.28,2.53)	(0.27,9.37)	(0.18,2.69)	(0.47,28.77)
T	13	14	15	16	17	18	19	20	21	22	23	24
13	—											
14	1.38 (0.06,51.93)	—										
15	1.02 (0,82.83)	0.73 (0,30.22)	—									
16	1.2 (0.01,81.91)	0.87 (0.01,28.42)	1.13 (0.01,355.7)	—								
17	1.67 (0.1,53.47)	1.19 (0.11,16.55)	1.64 (0.06,453.8)	1.37 (0.06,157.5)	—							
18	0.8 (0,60.67)	0.57 (0,23.85)	0.78 (0,382.2)	0.66 (0,137.1)	0.47 (0,13.78)	—						
19	1.73 (0.1,54.65)	1.24 (0.11,16.93)	1.66 (0.06,453.7)	1.44 (0.06,147.8)	1.03 (0.13,8.64)	2.17 (0.07,245)	—					
20	1.09 (0.02,55.55)	0.78 (0.02,20.27)	1.08 (0.01,417.7)	0.9 (0.01,141.3)	0.65 (0.02,11.14)	1.38 (0.02,231.4)	0.63 (0.02,11.02)	—				
21	2.31 (0.08,89.8)	1.64 (0.09,31.69)	2.28 (0.05,721.1)	1.9 (0.05,239.5)	1.38 (0.09,17.02)	2.91 (0.07,389.5)	1.33 (0.09,16.17)	2.16 (0.07,92.11)	—			
22	0.85 (0.04,28.15)	0.61 (0.05,8.75)	0.82 (0.03,223.2)	0.7 (0.03,77.15)	0.51 (0.06,4.38)	1.09 (0.03,129.2)	0.49 (0.06,4.24)	0.79 (0.04,27.89)	0.37 (0.03,6.01)	—		
23	0.85 (0,72.13)	0.6 (0,26.67)	0.84 (0,418.7)	0.72 (0,159.9)	0.5 (0,15.88)	1.08 (0,241.8)	0.49 (0,15.42)	0.78 (0,65.8)	0.36 (0,18.11)	0.99 (0.01,32.2)	—	
24	1.7 (0.13,45.45)	1.21 (0.17,12.8)	1.62 (0.08,401.2)	1.39 (0.09,122)	1.02 (0.19,5.88)	2.12 (0.09,215)	0.99 (0.18,5.53)	1.56 (0.12,44.86)	0.74 (0.08,9.24)	1.98 (0.36,12.92)	2.01 (0.09,257.5)	—

T: treatment

**Legend:

- | | | |
|---------------------------------|--|---|
| 1. SRP | 9. SRP + intensive maintenance | 17. SRP + SZ gel |
| 2. Control/no treatment | 10. SRP + non-intensive maintenance | 18. SRP + AV gel |
| 3. Intensive OHI | 11. OHI+ SRP+ intensive maintenance | 19. SRP + AZM gel |
| 4. Supragingival cleaning | 12. SRP + MTZ + AMX + intensive maintenance | 20. SRP + ALN gel |
| 5. Supragingival cleaning + AZM | 13. SRP + powered subgingival water irrigation | 21. SRP + SMV gel |
| 6. SRP + SDD | 14. SRP + aPDT | 22. SRP + CLM gel |
| 7. SRP + Doxy | 15. CHX rinse | 23. SRP + TET (topical) + non-intensive maintenance |
| 8. SRP + AZM | 16. SRP + CHX rinse | 24. SRP + CHX rinse + intensive maintenance |