Drug Safety and Effectiveness Network Report:

A Systematic Review with Network Meta-Analyses and Economic Evaluation Comparing Therapies for Hypertension in Non-Diabetic Patients

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May 2014

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- Dr. Brian Hutton led the development and authorship of the study protocol, performed network meta-analyses, generated summary graphics, and drafted the preliminary draft of the report.
- Fatemeh Yazdi coordinated the research staff and progress of the review, performed data collection of included studies, and performed data cleaning.
- Dr. Salmaan Kanji contributed to the development of the study protocol, interpretation of findings, and provided feedback on drafts of the clinical report.
- Mona Hersi and Jennifer Tetzlaff performed data collection of included studies, and contributed to drafts of the review protocol.
- Dr. Ferrán Catalá-López was a visiting trainee who contributed to preparation of data and figures for network meta-analyses, performance of network meta-analyses, and review of the clinical report.
- Drs. Dean Fergusson, Lise M. Bjerre, Andrea Tricco, and Sharon Strauss contributed clinical and methodologic expertise to the protocol development for this work and provided critical review of the drafts of the clinical report.
- Dr. Doug Coyle and Mrs. Cathryn Colye performed and drafted the economic evaluation component of thi review.
- Dr. David Moher contributed to the development of the study protocol, interpretation of findings, and provided feedback on drafts of the clinical report.
- Dr. Frans Leenen contributed his clinical insights as an expert in the field of hypertension to the drafting of the study protocol, interpretation of findings from all analyses, and reviewed drafts of the report.

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GLOSSARY	
Term	**Overview**
Bayesian Analysis	A statistical analysis conducted according to Bayesian statistical principles. It involves incorporation of existing information regarding the likelihood of an event (i.e., "priors") to estimate the likelihood based on additional information (i.e., posteriors").
Confidence interval	The interval in which a population parameter lies, based on a random sample of the population. The most commonly reported confidence interval is the 95% confidence interval.
Credible interval	In Bayesian statistics, an interval in which the actual value of a parameter of interest lies with a defined probability.
Deviance Information Criteria	A measure of model comparison and accuracy. Smaller values indicate a better-fitting model, with a difference greater than 4 or 5 indicating a much better-fitting model.
Meta-Analysis	Statistical synthesis of the results of individual studies that examine the same question to produce a single estimate of effect.
Network Meta-Analysis	An approach to evidence synthesis which allows for the combination of direct evidence (e.g. information from head-to-head trials of competing interventions) and indirect evidence (e.g. information from trials of a treatment against a control group such as placebo) to compare three or more treatments in a unified analysis.
Randomized Controlled Trial	A form of experiment in which participants are randomly allocated to receive one of the interventions under study. RCTs are commonly used to establish the efficacy and safety of medical interventions.
Systematic Review	A literature review which is conducted to address a focused research question which searches for, identifies, appraises, and synthesizes studies of relevance to the question. A type of review commonly used for evidence based medicine.
Incremental Cost Effectiveness Ratio (ICER)	A ratio measure that compares the difference in costs and clinical effects of two competing interventions; e.g. [total cost (trt 1)-total cost(trt 2)] / [Effect(trt1)-Effect(trt 2)]
Quality Adjusted Life Year (QALY)	An outcome measure which incorporates both quantity of life (mortality) and health-related quality of life (morbidity)
Dominance	Refers to situations in which one intervention is both less costly and more effective than its competitor(s).

ABBREVIATIONS USED IN THIS REPORT	
Abbreviation	**Full Terminology**
ACE-I	ACE-I Angiotensin Converting Enzime Inhibitor
ARB	Angiotensin Receptor Blocker
BB	Beta Blocker
CCB	Calcium Channel Blocker
TZD	Thiazide Diuretic
TZD+other active	Combination therapy involving a Thiazide diuretic and additional active agents
BB+other active	Combination therapy involving a Beta blocker and additional active agents
BB+TZD	Combination therapy involving a Beta Blocker and a Thiazide Diuretic
DIC	Deviance Information Criteria
NMA	Network Meta-Analysis
CrI	Credible Interval
ICER	Incremental Cost-Effectiveness Ratio
QALY	Quality Adjusted Life Year

Executive Summary

Background

Hypertension has been cited as the most common attributable risk factor for death worldwide, and an independent predictor of stroke mortality and ischemic heart disease mortality. Hypertension is a chronic yet modifiable condition which places increased stress on the heart for circulation of blood in the body, and it has been documented as a critical risk factor for clinically significant events including myocardial infarction, heart failure, stroke, peripheral artery disease, kidney disease, and death. It represents a preventable cause of early death in many countries. Reduction of elevated blood pressure is associated with reduction of clinically significant events such as those noted above. Evidence suggests there is a direct correlation between the magnitude of blood pressure reduction and the occurrence rate of such events. In addition to implementation of lifestyle changes including increased exercise, weight reduction, reduced alcohol consumption and dietary changes, there exists a number of classes of antihypertensive pharmacotherapies for use in clinical practice to manage elevated blood pressure. These include thiazide diuretics (TZD), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), beta blockers (BB), alpha blockers, and angiotensin receptor blockers (ARB). Furthermore, data from randomized trials suggests more than 66% of patients with hypertension cannot have their blood pressure adequately lowered using monotherapy, and so addition of a second agent (and sometimes third) may be required. Of primary importance in clinical practice is thus about the choice of therapies, and the sequence of interventions to minimize the risk of undesirable outcomes. The drugs are associated with different mechanisms of action, different harm profiles, and different costs. As such, the choice of agent is important. The optimal choice of first line agent is unclear. Several systematic reviews have explored the benefits and harms of pharmacotherapies for hypertension. However, the co-presence of comorbidities such as dyslipidemia, diabetes and so forth increase the risk of cardiovascular events, and a review comparing multiple treatments for patients free of diabetes has not been performed.. There remains a need to explore their properties in the sub-population of patients without diabetes.

Research Questions

1. *How does monotherapy with a thiazide diuretic compare to monotherapy with other pharmacotherapeutic agents (i.e. ACE inhibitors, CCBs, BBs, ARBs, etc) in patients without diabetes with hyptertension?*
2. *How do combination treatments involving a thiazide diuretic compare to combination treatments not involving a thiazide diuretic in patients without diabetes with moderate/severe hypertension or cardiovascular risk?*
3. *What is the relative cost effectiveness of monotherapies and combination therapies used to manage non-diabetic patients with hypertension?*

Methods

We leveraged the availability of a large number of existing systematic reviews and network meta-analyses to identify a large number of randomized clinical trials (RCTs) reporting on eight outcomes of interest: overall mortality, cardiovascular mortality, stroke, myocardial infarction, incident cancers, incident diabetes, sexual dysfunction, and depression. Studies performed in patients with hypertension were selected for inclusion if they included relevant antihypertensive treatments, if relevant outcomes were reported, and if the study included no more than a third diabetic patients or subgroup data on those without diabetes were available. Network meta-analyses of RCTs were used to explore the relative frequencies of each of the above outcomes.

Rigorous sensitivity analyses to account for clinical and methodologic heterogeneity (year of publication, mean patient age, gender distribution, use of background treatments, control group risk, and presence of industry funding) were performed to establish the robustness of findings. The objective of the economic component of this study was to determine the cost effectiveness of alternative pharmacological treatments for hypertension. Analysis used a similar approach to the model used within a previous technology assessment performed for the Canadian Agency for Drugs and Technologies in Health and used data from this review's network meta-analyses.

Summary of Findings

- **Evidence Base for Systematic Review and Network Meta-Analyses.** A total of 88 RCTs met our eligibility criteria. Amongst them, 60 reported on overall mortality (n=214,729), 39 on cardiovascular mortality (n=173,455), 37 on stroke (n=190,903), 27 on myocardial infarction (n=132,803), 15 on depression (n=47,746), 21 on sexual dysfunction (n=67,634), 25 on incident cancers (n=114,458), and 25 on incident diabetes (n=139,608). Trials consisted of patients with a mix of severities of hypertension, as well as corresponding variations in the use of co-medications and history of prior anti-hypertensive pharmacotherapies. Trial publication dates ranged from 1960-2011. Reporting of some study characteristics including presence of industry funding, patient ethnicity distribution and co-medication use was inconsistent. Studies involving ACE inhibitors (n=25), ARBs (n=12), BBs (n=20), CCBs (n=29), TZDs (n=27), placebo or no treatment (n=40), and an assortment of trials of combination therapies (BB + other active agents=2, BB + TZD=4, TZD + other active agents=10) were included in our analyses. Many studies were associated with use of background medications and step-up therapy.
- **Research Question 1: Comparison of TZD with other interventions**
    - There were no trials that directly compared all classes of antihypertensive agents. In terms of all-cause mortality, comparisons of TZD monotherapy with other monotherapies were inconclusive based on convential statistical significance at an alpha value of 5%, though comparison against BB suggested a potentially important benefit with TZD; only one statistically significant difference (favoring CCB over BB) amongst comparisons between different active monotherapies was identified. There was also a potentially important difference suggesting a benefit of CCB compared to BB for cardiovascular mortality, however most comparisons for this outcome were inconclusive, including all comparisons related to TZD. In terms of reducing incident strokes, TZD were statistically significantly more effective than BB, but were comparable with other monotherapies. TZD were potentially more effective than CCB, ARB and BB for reducing myocardial infarctions, however these comparisons were associated with high uncertainty; no evidence of a potential benefit compared to ACE-I was noted. In terms of clinically significant risks, no important differences were apparent except for incident diabetes. TZD were associated with a statistically significantly increased risk of incident diabetes compared to ACE-I, ARB and CCB.
    - Review of secondary measures of intervention effectiveness generated from network meta-analysis (i.e. treatment rankings) suggested TZD was the preferred monotherapy for stroke and MI incidence reduction, but TZD also were associated with the worst rank regarding incident diabetes. The analyses provide some clinical evidence of potential differences between therapeutic classes in non-diabetic hypertensive patients, which are not fully explained by clinical and methodologic heterogeneity in the included trials.

- **Research Question 2: Comparison of TZD-based combination therapy interventions with other combination therapy interventions**
- We classified combination regimens in our treatment networks according to the groups of TZD+other active agents, TZD+BB, abd BB+other active agents. A relatively small number of studies involving combination therapy. We also did not have evidence in our treatment networks on some combination regimens relevant to clinical practice including regimens such as ACE-I+CCB and TZD+CCB.
- Analyses for mortality outcomes, stroke and MI all demonstrated strong and statistically significant benefits of TZD+other active agents compared to most other monotherapies and combination therapies. The size of the effects associated with this regimen exceeded expectations; given challenges in the evidence base (i.e. few head-to-head studies, sample size, indirectness of evidence, and so forth), the size of these benefits should be interpreted cautiously in terms of decision-making.
- Past clinical guidance has suggested that therapy with BB+TZD is effective, however relatively few data were eligible. BB+TZD has demonstrated clinical benefits previously, however some clinical guidelines note this regimen may be associated with concerns regarding incident diabetes while other combinations (e.g. TZD+ACE-I, TZD+ARB, ACE-I+CCB) are also effective.
- **Research Question 3: Comparing the Cost-Effectiveness of Competing Monotherapy and Combination Therapy Interventions**
    - The economic analysis found little to choose from between each of the drug treatments in terms of effectiveness with results primarily driven by drug costs. Treatment with BB in combination with TZD is the most cost effective treatment option for all men and women aged less than 75. For women aged 75 and over, ARB in combination with TZD is the most cost effective treatment option.

Strengths and Limitations of this Work

- Our network meta-analyses were based on a large number of trials and participants. However, the variation in the number of studies included for analysis for each outcome (range 15-60 depending on outcome) suggests a lack of transparency of reporting of outcomes and possibly biasing the results due to selective reporting. When dealing with rare outcomes, particularly harms, this can lead to wide uncertainty around meta-analytic estimates. We also excluded several large RCTs because they included a larger proportion of diabetic patients than allowed based on our inclusion criteria, and subgroup data from non-diabetic participants was not reported. Review of on-treatment blood pressure changes from included trials was not a planned outcome for our review, however these may provide further understanding of findings observed.
- Use of background/prior antihypertensive therapies and the use of step-up therapy within studies complicated classification of regimens received. We followed procedures for treatment classification in line with previous network meta-analyses by classifying by first treatment received. However, this may lead to some misunderstanding of agents' effects, and may be a function of variation of blood pressure targets across studies. Clear comparison of monotherapies and combination therapies was often not possible due to use and mixed clarity regarding the use of prior medications.
- Reporting of study characteristics including duration of follow-up, participant ethnicity, presence of industry funding and other characteristics was inconsistent across included trials. Variations in patient characteristics over time, the use of co-interventions, and

other features were present. To the extent possible, we pursued sensitivity analyses to establish the robustness of our findings, which appears strong.

- While several antihypertensive agents belong to each class of medication, the degree to which these were reflected at the agent level was mixed across studies. While our analyses were performed at the drug class level, we recommend readers also study the agents used in the underlying trials if there exists an interest in particular agents. Our range of agents reflected within each class may also be more narrow than other network meta-analyses in this field because our research questions required additional restriction criteria related to diabetes which was associated with the exclusion of assorted trials.
- We identified minimal study data meeting our inclusion criteria for alpha blocker treatments. A recent review highlights that the majority of study information for this class has evaluated changes in blood pressure and not the hard outcomes that were of interest in our systematic review. As a consequence of this and our inclusion criteria regarding diabetes, we could not evaluate its benefits in our networks.
- Given limited resources available for this assessment, a full economic analysis incorporating uncertainty (i.e. both deterministic and probabilistic models) was not possible. The economic analysis is restricted to a patient population without previous event history, however a more in depth analysis of variability would explore the impact of prevalent disease on the cost effectiveness of treatments. A more in depth analysis would also explore differential results in terms of cost effectiveness within drug classes.

Conclusions

- Based on findings from network meta-analyses, we performed class level comparisons of both interventions across a range of both effectiveness and harms outcomes with a focus on non-diabetic patients. While all agents showed evidence of benefit, not all agents consistently showed statistically significant improvements across measures of overall mortality, cardiovascular mortality, stroke and myocardial infarction. Monotherapy with thiazide diuretics was comparable in terms of benefit to other monotherapy interventions, with summary estimates suggesting some potentially stronger benefits for stroke and MI.
- Combination therapy involving thiazide diuretics with other active agents was associated with the largest treatment effect compared to no treatment for overall mortality, cardiovascular mortality and stroke, and demonstrated statistically significant benefits over other classes in many comparisons; much less data for this intervention was available for myocardial infarction. Interpretation of the benefits of this regimen should be made carefully, as for several outcomes these estimates are based on a small number of head-to-head RCTs and are informed by indirect comparisons.
- From a harms perspective, the reputation of thiazide diuretics to increase the risk of incident diabetes was evident in our analyses. We did not find information suggesting any increased risk of cancers or depression based on the data from our included trials.
- The economic analysis found little to choose from between each of the drug treatments in terms of effectiveness with results primarily driven by drug costs. Treatment with BB in combination with TZD is the most cost effective treatment option for all men and women aged less than 75. For women aged 75 and over, ARB in combination with TZD is the most cost effective treatment option.

1. Clinical Background

Hypertension has been cited as the most common attributable risk factor for death worldwide, and an independent predictor of stroke mortality and ischemic heart disease mortality.[1,2] At a national level, data from the Public Health Agency of Canada highlight several impressive figures which truly show the burden of disease associated with hypertension:[3]

- In 2006-2007, more than 1 of every 5 adult Canadians suffered from high blood pressure.
- In 2007, more than 21.1 million physician visits were related to high blood pressure.
- More than any other indication, high blood pressure is responsible for extremely high prescription counts (more than 4 million per month).

Blood pressure is a measure of the pressure which blood places against the walls of blood vessels during circulation.[4] It is typically measured using two numbers, systolic blood pressure (SBP; normal values <130 mmHg) and diastolic blood pressure (DSP; normal values <80-85 mmHg). When SBP rises above 140 mmHg or DSP rises above 90 mmHg, the patient is considered to have high blood pressure (i.e. hypertension).[4,5] Hypertension is considered a chronic yet modifiable condition which places increased stress on the heart for circulation of blood in the body, and it has been documented as a critical risk factor for clinically significant events including myocardial infarction, heart failure, stroke, peripheral artery disease, kidney disease, and death. It represents a preventable cause of early death in many countries worldwide.

The prevention and control of elevated blood pressure is associated with reduction of clinically significant events such as those noted above. Evidence suggests there is a direct correlation between the magnitude of blood pressure reduction and the occurrence rate of such events, and treatment is geared toward lowering blood pressure to below 140 SBP/90 DSP in most patients; treatment of hypertension in patients younger than 60 years of age reduces the risks of stroke and coronary events by totals of 42% and 14%, and in patients 60 or more years of age reduces the risk of stroke by 35%, coronary events by 18%, cardiovascular mortality by 36%, and overall mortality by 15%.[6,7] In addition to implementation of lifestyle changes including increased exercise, weight reduction, reduced alcohol consumption, dietary changes, lowering of sodium intake and stress management, there exists a number of classes of antihypertensive pharmacotherapies for use in clinical practice to manage elevated blood pressure; these include diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), beta blockers (BB), alpha blockers, and angiotensin receptor blockers (ARB). Guidelines described by the Canadian Hypertension Education Program (CHEP)[5] in 2012 outline that:

- *Initial therapy* should consist of monotherapy using any one amongst thiazide diuretics, beta-blockers, ACE inhibitors, long-acting calcium channel blockers or an angiotension receptor blocker (ARB).
- *Second line therapy* (addition of a second agent) should be considered if the target blood pressure is not achieved with monotherapy, choosing amongst the agents considered for first line monotherapy. Specific combinations (i.e. an ACE inhibitor with an ARB or a beta-blocker with nondihydropyridine calcium channel blockers) are noted as best avoided. Many patients require more than one medication to control their hypertension, and many possible combinations are possible.
- *Combination therapy* may be considered as first line therapy in patients where SBP is 20 mmHg above the target range or DBP is more than 10 mmHg above the target range, however caution must be taken to do so where subjects may poorly tolerate this change.

- **Data from randomized trials suggests that more than 66% of patients with hypertension cannot have their blood pressure adequately controlled using monotherapy, and so addition of a second agent (and sometimes third) may be required.[8]**

The choice of therapy and sequence of interventions are important considerations to minimize the risk of undesirable outcomes while maximizing efficacy and adherence. The drugs are associated with different mechanisms of action, different harm profiles, and different costs. The optimal choice of first line agent remains unclear, as some suggest thiazide diuretics are best,[9,10] while others suggest calcium channel blockers should be considered as first line therapy in patients over 55 years of age or of Caribbean or African descent (with ACE inhibitors to be used in those of younger ages).[11] In Canada, all but alpha blockers are considered to be reasonable first line therapies, with patients' demographics and comorbidities playing a role in selection along with costs and coverage.[5]

Context of this Review. The current Drug Safety and Effectiveness Network (DSEN) query emerged based on a recent claim of a systematic review suggesting that thiazide diuretics are inferior to combination therapy regimens. This claim conflicts with past published evidence and practice guidelines from the Canadian Hypertension Education Program (CHEP).

The current query asks for an assessment of the effectiveness (and cost-effectiveness) of thiazide diuretics, ACE inhibitors and combination antihypertensive therapy, with a particular interest in the outcomes of time in target blood pressure range, drug adherence, and complications of hypertension. To maximize clinical relevance of this work, we expanded the question to also consider other classes, namely calcium channel blockers, beta blockers, angiotensin receptor blockers (ARBs), alpha blockers, and placebo or no treatment (for the purposes of conducting indirect and mixed comparisons).

2. Research Questions

In non-diabetic patients with hypertension:

1. *How does monotherapy with a thiazide diuretic compare to monotherapy with other pharmacotherapeutic agents (i.e. ACE inhibitors, CCBs, BBs, ARBs, etc) in non-diabetic patients with hyptertension?*
2. *How do combination treatments involving a thiazide diuretic compare to combination treatments not involving a thiazide diuretic in non-diabetic patients with moderate/severe hypertension or cardiovascular risk?*
3. *What is the relative cost effectiveness of monotherapies and combination therapies used to manage patients with hypertension?*

3. Methods/Design

Prior to beginning this review we published our protocol describing our planned methodology[12] and registered with PROSPERO (CRD42013004459).

3.1 Literature Search and Study Selection

Based on existence of a large number of existing reviews in hypertension that could be leveraged, a primary search for randomized trials was not performed. We used a staged approach to study identification, beginning with examining Cochrane reviews published in 2005 and onward as well as network meta-analyses published at the time the review was initiated to identify eligible randomized controlled trials (RCTs). We then searched Medline to identify other relevant systematic reviews in this field and compared their lists of included studies with our database of eligible trials in reverse chronologic order by year until the yield of new studies was very low. This literature search is provided in **Appendix 1**, was designed by an experienced information specialist and subsequently peer reviewed by a second independent information specialist according to PRESS criteria.[13] To identify additional randomized trials published outside of the time periods of the reviews which were scanned, we compiled a listing of unique Medline identifier numbers of each of our eligible trials identified from the steps above, and subsequently performed a Related Articles search in Medline (dating back 10 years to 2003); results were limited to the top five general medicine journals (Journal of the American Medical Association, New England Journal of Medicine, British Medical Journal, Annals of Internal Medicine, Lancet) and related specialty journals based on impact factor rating. These were subsequently screened independently by two reviewers for eligibility, first at the abstract level and then at the full text level for those considered potentially eligible. The process of literature selection has been reported using a flow diagram.

3.2 Study Eligibility Criteria

Eligibility criteria for study selection are described here according to the Population-Intervention-Comparators-Outcomes-Study design (PICOS) framework. Specifically, published studies comparing relevant interventions in human subjects were eligible if the crieria outlined in **Table 1** were met.

The DSEN query asked how monotherapy with a thiazide diuretic may compare to combinations of the various above agents. To address this question, based upon clinical expertise from our team and the treatments compared within our selected collection of trials, we selected three categories of combination therapy for our network meta-analyses: beta blockers combined with thiazide diuretics (denoted in figures as BB+TZD), thiazide diuretics combined with other active agents (TZD+other active), and beta blockers combined with other active agents (BB+other active).

Only English language study reports were included. Past research suggests that limiting included studies to those reported in English does not introduce bias into the summary estimates from meta-analyses.[14,15]

Table 1: Study Eligibility Criteria for Inclusion in the Review	
Selection Criteria	**Description**
Population	Non-diabetic patients with hypertension were of interest. Either subgroup data had to be available for this group in the trial, or a predominance of patients with hypertension (>66.6%) had to be non-diabetic. No restrictions were used regarding gender or patient age. Studies of patients with history of acute stroke, acute MI, or heart failure were excluded.
Intervention and Comparators	We considered studies involving the comparison of agents from any of the following classes of pharmacotherapies commonly used to treat hypertension: thiazide diuretics (TZD); ACE inhibitors (ACE-I); calcium channel blockers (CCB); alpha blockers (AB); beta blockers (BB); angiotensin receptor blockers (ARB); and combinations of these therapies. Placebo/no treatment were also included to maximize the inclusion of indirect evidence. A class of 'other therapies' was also included to address other agents appearing within included studies.
Outcomes	o Overall and cardiovascular mortality o Myocardial infarction (MI) and stroke o Clinically important side effects: sexual dysfunction, depression, incident cancers, incident diabetes
Study Designs	Randomized controlled trials of 1 year duration or longer were eligible.

3.3 Data Collection and Risk of Bias Assessment

Primary data collection of included studies was performed independently by two reviewers using a standardized electronic data collection form. Distiller SR (Ottawa, Canada) software was used to compare collected data for accuracy and agreement, with disagreements being settled by discussion. For assessing risk of bias, all relevant RCTs were reviewed using the Cochrane Risk of Bias (RoB) tool which evaluates seven domains including: sequence generation, allocation concealment, blinding, missing outcome data, selective outcome reporting, attrition, and "other sources of bias." Any disagreements in the assessments were resolved through discussion or by third party adjudication. We also collected the following additional information: age, gender, race, baseline blood pressures, the frequency of cross-overs and dropouts (and associated reasons).

3.4 Classification of Study Populations

Our primary data analyses considered all trials of all patients meeting our eligibility criteria together in one treatment network; in addition to this approach, we also considered sensitivity analyses we felt worthwhile to account for variations in patient severity. While the presence of hypertension is a major risk factor for cardiovascular disease, it does not fully account for the patient's overall risk for clinically important events. Other aspects of a patient's clinical profile may be considered in order to prevent and control morbidity and mortality. With regard to the set of included randomized trials, some were conducted in patients with hypertension who are at increased risk of cardiovascular events due to current or past comorbidities and medical

histories. We classified studies into the categories of 'low' versus 'moderate/high' risk in collaboration with our clinical experts (FL, SK, FCL). A study was considered to have been conducted in a moderate or high risk population if it met the following criteria:

- the authors of the publication defined the population at high-risk (in title and/or abstract); or
- baseline characteristics and study eligibility criteria provided in the report indicate the patient population consisted of at least a proportion of subjects who are adult hypertensive patients (mean age $\geq$ 55 years) with a history of cardiovascular disease or end organ damage plus as well as another cardiovascular risk factor (e.g. elevated cholesterol, obesity, smoking, left ventricular hypertrophy, diabetes mellitus).

We have provided our classification for each study and associated rationale in **Appendix 2**.

3.5 Classification of Interventions

Our analyses were performed at the class level with the following categories: placebo or no treatment, ACE-I, ARB, BB, CCB, TZD, BB+TZD, TZD+other active agents, BB+other active agents. Our clinical experts indicated that in many trials, after study participants are randomized to an initial treatment, treating physicians may add additional anti-hypertensive pharmacotherapies to their regimen according to pre-determined protocols for step-up therapy to achieve blood pressure targets. In such cases, each study arm was classified based on the original treatment strategy for which randomization was performed. This approach has been used in prior network meta-analyses in this clinical area, and we compared our classification of trials with existing publications of network meta-analyses to avoid discrepancies in classification. Thus in summary, trial participants were analyzed according to the treatment group they were randomized, regardless of subsequent changes to treatment. While we have used the terminology *monotherapy* and *combination therapy* in this report in relation to randomized treatments received, it is important to note that given the above reasons that study participants' prior treatments may often mean that true monotherapy is not present, and other agents may be in use amongst patients in study treatment groups.

3.6 Approach to Meta-Analysis

As mentioned above, analyses were conducted at the drug class level. We begin with a narrative overview of included studies in the review, focused on discussion of the degree of clinical and methodologic homogeneity present. This includes overview of findings from risk of bias assessments, as well as other important differences between studies in terms of patient characteristics, study design, statistical analysis, and so forth. When judged appropriate based on homogeneity and similarity of studies with regard to important effect modifiers of outcome, network meta-analysis (NMA) was performed.[16] NMA is an approach to evidence synthesis which allows for the combination of direct and indirect evidence to compare three or more treatments in a unified analysis. Indirect comparisons between treatments A and B based on a common comparator C where no trials of A versus B exist (i.e. no direct evidence) but trials of A versus C and B versus C exist (i.e. indirect evidence) were originally proposed by Bucher et al,[17] and Lumley[18] and Lu and Ades[19] subsequently developed extensions of this methodology. In

addition to estimating all pairwise comparisons between treatments in a network, this technique can also be used to estimate probabilities of treatment of superiority to rank the treatments.

3.6.1 Approach to Conduct of Network Meta-Analyses

We performed Bayesian network meta-analyses as outlined by Dias et al[20] using a common heterogeneity parameter to synthesize information for each outcome under study. Both fixed and random effects models were fit based on burn-in iterations of 40,000 or more, and parameter estimates were based on additional samples of 40,000 or more. Model fit was performed by comparing the total number of unconstrained data points (i.e. total # of treatment arms in the analysis) to the residual deviance for each analysis, while comparisons between fixed and random effects models were based on deviance information criteria (DIC; a difference of 5 points or more was considered an important difference between models, where a smaller value suggests improved model fit). To be conservative, we based our interpretations on random effects models unless an important difference in model fit was found suggesting otherwise. All pairwise comparisons between competing interventions were expressed as odds ratios (OR) with corresponding 95% credible intervals (CrI). Consistency of results from direct and indirect information in the network under study was evaluated by comparison of DIC from an inconsistency model with the DIC from the corresponding consistency model.[21] Trials with zero events were adjusted by adding 0.5 to the numerator and 1 to the deninator for each treatment group. In addition to estimation of odds ratios, we also estimated median treatment rankings, probabilities of superiority for each treatment, and Surface Under the Cumulative Ranking (SUCRA) values. All network meta-analyses were performed using Winbugs software version 1.4.3 (MRC Biostatistics Unit). Vague prior distributions were assigned for parameters throughout the models for meta-analysis, and we assessed convergence of all models by fitting multiple chains and exploring Gelman Rubin trace plots. Network diagrams summarizing the geometry of evidence available for each clinical outcome were generated using Stata 13.0 software, and functions created and reported by Chaimani et al.[22]

3.8 Addressing Clinical & Methodologic Heterogeneity

In addition to our primary unadjusted analyses, we also planned several analyses to address potentially important clinical and methodologic heterogeneity in the included studies.

- **Clinical sensitivity analyses**. Several clinical characteristics were of interest in this work given their status as risk factors for hypertension and related clinical outcomes. We attempted to pursue network meta-regression analyses to explore their impact where feasible. These characteristics included the following:
    - **Year of study publication.** The use of co-medications is not consistently reported from study to study, and changes in clinical practice over time (for example, use of statin therapy or aspirin) may have an important impact on outcomes. Analysis to adjust for year of publication represents an effort to adjust for important changes over time (whether related to co-medication or other unknown factors).
    - **Mean age.** Increased age may be associated with an increased occurrence of the outcomes of interest. Adjustment for mean age across studies may help account for this influence in our analyses.

- **% Males.** Differences exist between men and women with regard to the risks of the prevalance, risk, and outcomes of cardiovascular disease. This includes hypertension and possibly the effects of anti-hypertensive agents.[23,24] Adjustment for % male participants across studies may help account for this influence in our analyses.
- **Background therapy.** In the effort to address for the use of previous/background hypertension medications, we performed a meta-regression analysis where we classified studies as using background treatment if 33.3% or more of patients were reported to be receiving additional medications, and otherwise classified them as having patients as non-recipients of background medications.
- **Control group risk.** Variations in the rate of outcomes across the control groups of different studies (for example different rates of death in untreated patients) can impact findings from network meta-analysis; adjustment for these variations can be important in some cases. We performed a control group risk for each outcome to address this possibility.
- **Ethnicity.** Because a breakdown of ethnicity was often not reported, sensitivity analyses attempting to adjust for this covariate would have consisted of notably smaller numbers of studies and thus were not performed. We considered sensitivity analyses excluding studies which were of entirely one particular ethnicity to maximize generalizability of findings.
- **Alternative geometries.** As suggested by our clinical experts due to similarity of treatments, we also considered an alternative arrangement of our class level structure of treatment networks in sensitivity analyses; this involved collapsing of ACE-I and ARB to be included into one node in our networks, as well as collapsing of BB+TZD with BB+other active into one node.

- **Methodologic sensitivity analyses.** Results from assessment of the risk of bias of included studies were incorporated in our work. A meta-regression analysis based on the presence/absence of industry funding was explored; where funding was not reported or funding was a combination of public and private funding, we grouped the study as not being industry funded. We also assessed the findings from our analyses from the perspective of considering the presence of trials of large sample size which were judged to have elements at high risk of bias; sensitivity analyses were considered accordingly where concerns were noted.

Findings from all sensitivity analyses were compared with estimates generated from our primary analyses. Detailed tables provided in the appendices to the report provide summaries of findings from all senstivity analyses in relation to our primary findings.

3.9 Reporting of findings from analysis

Graphical and numeric presentations of findings are provided to convey the findings of our work. For network meta-analyses, we have included the following:

- ***Treatment network diagrams*** which show the geometry of available evidence for all possible treatment comparisons in terms of the included treatments with available data, the numbers of studies supporting each comparison of treatments, and the included numbers of subjects.

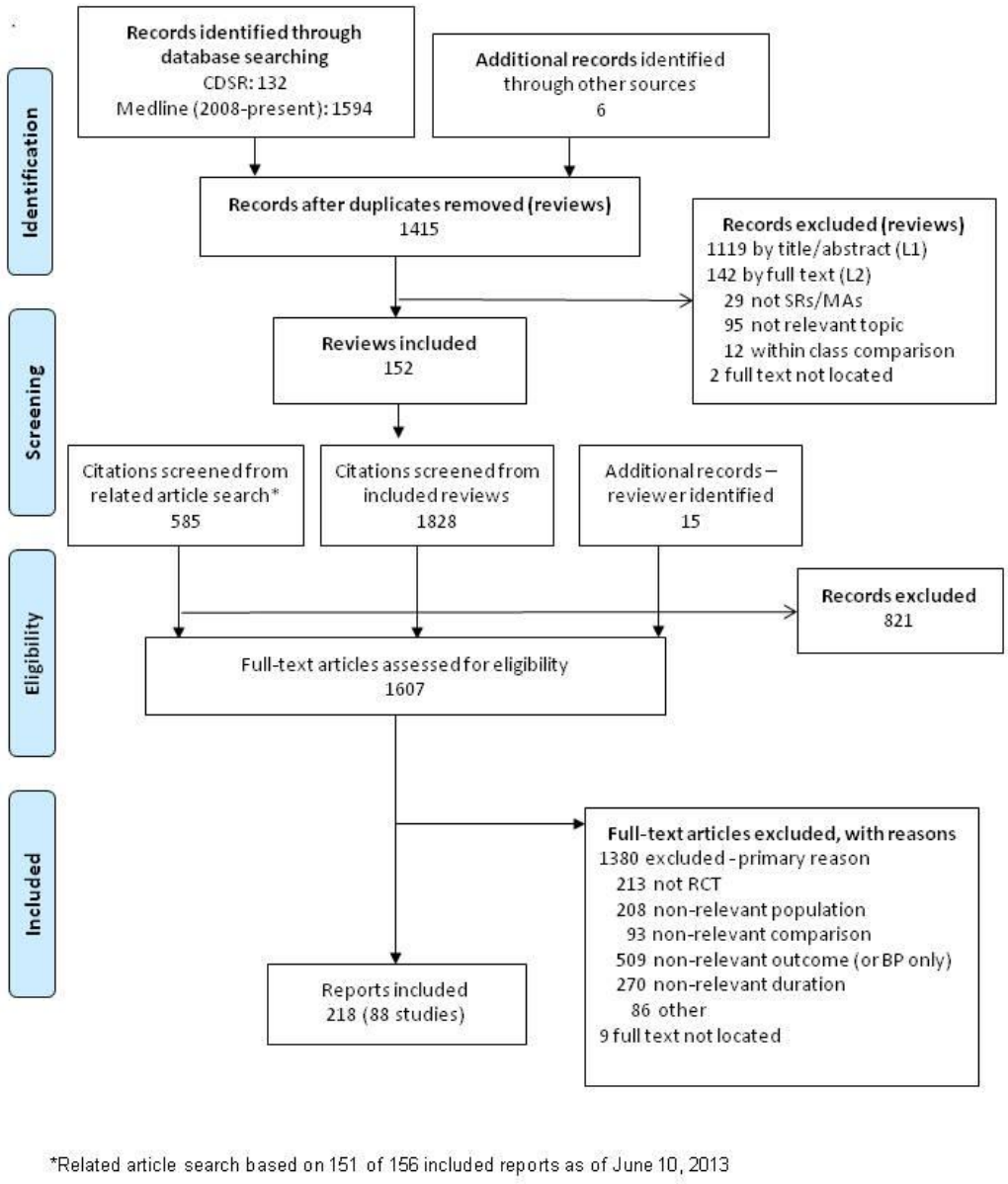
- ***Forest plots*** which provide summary point estimates and corresponding 95% credible intervals for all pairwise comparisons against our reference group, estimated using network meta-analysis. In this review, odds ratios greater than 1 for comparisons against the reference treatment suggest an increased risk of harms. We use the notation of 'n' and 'N' to reflect the numbers of events and total numbers of patients studied for each intervention in the treatment network.
- ***League tables*** which summarize all possible comparisons between treatments in the network. In these figures we have used a combination of yellow coloring and bolded font to highlight statistically significant differences.
- ***SUCRA values and median treatment rankings*** which provide an additional summary measure of treatment risk which can be considered as a secondary quantity to support pairwise comparisons presented in the above forest plots and league tables. In this review, SUCRA values (range 0-100%) nearer 100% and treatment rankings nearer 1 suggest a lower risk of harms. We note that these quantities should not be considered in isolation to draw findings based on ongoing methods research which has addressed some concerns with such an approach.
- ***Supplemental Appendices*** have also been included which document our extensive sensitivity analyses using a network meta-regression approach. These follow our included tables documenting characteristics of the included trials.
- In addition to providing the above information through tables and figures, we have also provided associated brief text summaries to guide interpretation regarding the differences that were identified.

4. Systematic Review Results

4.1 Literature Search Results

Our search for relevant reviews yielded 1,415 unique records, of which 152 were ultimately included (see PRISMA flow diagram). From these reviews, 1,828 unique records were identified from the included study lists, and - where relevant - excluded studies lists and were uploaded for screening. In addition, 585 records were uploaded from the PubMed Related Articles search based on 156 reports included as of June 10, 2013; 15 additional reports were identified by reviewers. Overall, 1,607 full text reports were reviewed and a total of 88 unique studies.[25-112] described in a total of more than 200 published reports were included.[25-231]

FIGURE 1: PRISMA Flow Diagram for Study Selection Process



The above figure provides a summary of our study selection process based on the modified approach to searching described in Section 3.1.

Several large, well-known trials of anti-hypertensive medications were excluded from our systematic review because they failed to meet one or more of our eligibility criteria. **Table 2** provides an overview of trials with more than 1,000 participants.

Table 2: Established RCTs Excluded from our Review

Study	Comparison	# Randomized	Reason for Exclusion
Braunwald et al, the PEACE Trial (2004)[232]	ACE-I versus placebo	8,290	Outcomes in hypertension sub-population reported only as a composite outcome measure
Pfeffer et al, the CHARM trial (2003)[233]	ARB versus placebo	6,446	Outcomes not reported in hypertension sub-population
Jamerson et al, the ACCOMPLISH trial (2008)[234]	ACE-I+CCB versus ACE-I+ TZD	11,506	>33.3% diabetic participants (60%), and outcomes not reported for subgroup
Ogihara et al, the CASE-J trial (2008)[235]	ARB versus CCB	4,728	>33.3% diabetic participants (43%), and outcomes not reported for subgroup
Suzuki et al, the E-COST trial (2005)[236]	ARB versus conventional treatment	4,238	>33.3% diabetic patients (50%), and comparator unclear (described as conventional treatment involving anything other than ACE-I or ARB)
Hansson et al, the CAPPP trial (1999)[237]	ACE-I vs conventional treatment	10,985	Comparator group unclear (described as conventional treatment involving diuretics, beta blockers, or both)
Lewis et al, the IDNT trial (2001)[238]	CCB versus ARB versus placebo	1,715	>33.3% diabetic patients (100%)
HDFP Study Group, the Hypertension Detection and Follow-up Program (HDFP) Study (1979)[239]	Stepped care versus referred care	10,940	Intervention group medications unclear
Black et al, the CONVINCE trial (2003)[240]	CCB versus BB versus TZD	16,602	Comparator group unclear (described as conventional treatment involving choice of either BB or TZD)
Yusuf et al, the PRoFESS trial (2008)[241]	ARB versus placebo	20,332	Patients were excluded if a stroke was experienced <90 days prior to study enrollment

4.2 Summary of Study Characteristics

A short narrative summary of study characteristics is provided next. **Table 3** provides an overview of key clinical and methodologic features of the included RCTs, while tables in the appendices provide comprehensive documentation of the characteristics of studies included in the review.

4.2.1 Primary Study Characteristics

Studies were published between the years 1960-2011 (median 1999), and were associated with a median sample size of 553 participants (range 22-42,424). Overall, 50 studies were associated with partial or full industry funding. Study follow-up was not consistently reported in terms of mean or median patient follow-up; 27 of the included studies were associated with mean or median follow-up of between 3-5 years, while durations above and below this range were also reported.

4.2.2 Treatment Regimens Compared

Randomized evidence was available for a total of 12 distinct treatments: ACE-I (25 studies; 18,737 patients); BB (20 studies; 41,920 patients); CCB (29 studies; 55,547 patients); alpha blockers (1 study; 110 patients); TZD (27 studies; 40,158 patients); ARB (12 studies; 22,657 patients); placebo/ no treatment (40 studies; 45,664 patients); and combination therapies consisting of BB+TZD (4 studies; 2,956 patients), TZD + other active agents (10 studies; 9,815 patients), BB + other active agents (2 studies; 5,561 patients), ACE-I + CCB (2 studies; 136 patients), and other active regimens (7 studies; 1,838 patients). Across studies, classes varied with regard to the agents that were used. The following agents were used in one or more studies: ACE-I: enalapril, lisinopril, captopril, quinapril, ramipril, fosinopril, benazepril; ARB: valsartan, candesartan, losartan; BB: atenolol, metropolol, propranolol, acebutolol, oxprenolol; CCB: nifedipine, diltiazem, amlodipine, verapamil, lacidipine, felodipine, isradipine, nicardipine; TZD: chlortalidone, trichloromethiazide, bendroflumethiazide, hydrochlorothiazide, indapamide; Other: reserpine, hydralazine, amiloride, aliskiren.

4.2.3 Patient Populations

Amongst our included 88 RCTs, totals of 29 and 59 studies were categorized to have been performed in patients with lower versus moderate/high cardiovascular risk patients, respectively. Mean age of participants ranged from 44 to 83.8 years (median 58.5 years), while the proportion of males ranged from 25.8% to 100% (median 55%). The distribution of participant ethnicity was not consistently reported across trials; nine studies were reported in only Caucasian patients, two in black patients, six in only Asian patients and one in only Hispanic patients while the remainder consisted of a combination of patient ethnicities; a total of 43 studies failed to report this information. Concomitant use of medications such as aspirin or statins was indicated in 20 studies. We have provided a summary table of patient demographics in **Appendix 2** which provides a detailed account of key study characteristics, including mean age, propotion of male subjects, patient comorbidities, and so forth. Unfortunately for some characteristics, sufficient information on risk factors of interest for sensitivity analyses was not always reported, limiting the ability to explore the impact of heterogeneity in some cases.

In 9 of 88 included studies, the proportion of patients with diabetes could not be ascertained due to insufficient demographic information. Five of these studies excluded insulin dependent or

uncontrolled diabetics[62,72,86,102,112], two studies excluded patients with type I diabetics,[62,70] two studies with patients having renal failure reported including <10% with diabetic neuropathy,[82,109] and one study excluded patients with diabetes taking more than two antihypertensive medications.[64] A total of 21 studies did not provide any information about baseline diabetes. In two studies (the ALLHAT study[51] and the TRANSCEND study[63]), >33% of patients had diabetes at baseline. However, outcome data for the subgroup of hypertensive patients without diabetes was provided and was used in this review. Twenty eight studies excluded patients with diabetes. Less than 33% of the study population in the remaining 28 studies had diabetes (median 11.5%, range 1%-32.5%).

Table 3: Overview, Characteristics of Included Studies

Trial Characteristic	Categories	# of Included Studies
Patient population	Moderate/high risk	59
	Low risk	29
Industry sponsorship (partial or full)	#yes/#no/# partial or mixed/#not reported	36/15/13/24
Year of Study Publication	2000-present	41
	1990-1999	28
	1980-1989	13
	1979 or earlier	6
Sample size	Median and range	553 (range 22-42,424)
Duration of Follow-up (years)	Range	11.7 months to 7 years*
Mean subject age (years)	Median and range	58.5 (44-83.8)
	# >70 / # 60-69 / # 50-59 / # <50	16/21/28/15**
Ethnicity	# caucasian only/blacks only/ other	9/2/35
	% blacks, median and range	19.55% (0%-100%)***
	# not reported	43
% male subjects	Median and range	55% (25.8%-100%)
	# not reported	5
Use of co-medications (e.g. statin, aspirin)	# studies indicating use	20
# with past use of antihypertensive medications	No participants/All participants/Mixed/ Not reported	8/2/55/23

*denotes in 37 studies, follow-up duration was unclear; **denotes 8 studies did not report average age; ***denotes only 21 studies reported % blacks

4.2.4 Outcome Definitions

Outcome definitions were relatively consistent across included trials. Cardiovascular death was defined to include deaths due to stroke, myocardial infarction, coronary heart disease, left ventricular failure, and other related events. Analyses related to both stroke, myocardial infarction and cancers were performed using studies that counted both fatal and non-fatal events. Incident diabetes definitions were often based on fasting blood glucose levels and in a small number of studies were self reported. When defined, cases of depression were defined according to impact on regular daily activities or were assessed by questionnaire. Sexual dysfunction was mostly defined according to the presence of erectile dysfunction, impotence or decreased libido.

4.2.5 Risk of Bias Evaluation

For risk of bias assessments, low, unclear and high risk of bias are identified for different sources of bias in the design of the study. For the 7 considered sources of bias, the majority of our included outcomes ranked as being of moderate risk of bias based on achieving a score of low or unclear risk of bias for a minimum of 5 of the 7 criteria. The most common reasons for assessing an outcome as being at a high risk of bias were completeness of outcome data, blinding (particularly when assessing depression, sexual dysfunction, and adherence to randomized treatments), and funding status.

As can be seen in the summary of risk of bias evaluations provided in **Appendix 2**, random sequence generation was adequate in 39% of included studies and unclear or not reported in the remaining 61%. Allocation concealment was adequate in only 24% of studies, with the remaining 76% failing to provide sufficient information. Masking of randomized regimen (double or triple blinding) was reported in 35% of included studies while in 55% blinding of patients and participants was either not undertaken or broken before the study end. Additionally, 35%, and 11% of the studies were assessed as low risk of bias for completeness of outcome data and selective outcome reporting, respectively. Imbalances in demographics or confounding factors (e.g. baseline BP, proportion with comorbidities, medication used at baseline, etc.) were identified in 8% of the studies while 89% did not report sufficient information regarding possible confounding factors (as pre-specified) or baseline demographics.

4.2.6 Amount of Information by Clinical Outcome

Table 4 summarizes the number of studies reporting data for each clinical outcome of interest. There was considerable variation in the number of studies included across outcomes. This variation in reporting from study to study and the broad range in the sample size of included trials was associated with highly variable totals of included participants across meta-analyses. Individual numbers of patients and events for each intervention class are reported in subsequent sections.

Table 4: Reporting of Outcomes In Included Studies

Outcome	# studies	Total # participants	Total # of events	Aggregate Event rate
Overall Mortality	60	214,729	15,575	7.3%
Cardiovascular Mortality	39	173,455	6,495	3.7%
Stroke	37	190,903	6,982	3.7%
Myocardial Infarction	27	132,803	4,933	3.7%
Cancers	25	114,458	5,730	5.0%
Depression	15	47,746	3,126	6.6%
Incident Diabetes	25	139,608	12,542	8.9%
Sexual Dysfunction	21	67,634	3,328	4.9%

4.3 Results from Meta-Analysis

4.3.1 Findings from Pairwise Meta-Analyses

Prior to pursuing network meta-analyses, we performed pairwise meta-analyses for all treatment comparisons in our network to explore for statistical heterogeneity and to note findings from syntheses of direct meta-analyses prior to pursuing network meta-analyses. We have included these results in **Appendix 3.** We do not comment on these summary estimates in our main text.

4.3.2 Findings from Network Meta-Analyses

Overview

The following sections provide summaries of findings for each of the outcomes studied in this systematic review studied using network meta-analysis. Treatment network diagrams are used to summarize the interventions with available data and the number of trials available for each comparison of interventions. Due to inconsistent outcome reporting and related implications for worsening of model fit, the treatment regimen of ACE-I+CCB was not included in our network meta-analyses. We provide summaries of findings to comment on statistically significant differences between interventions compared (i.e. summary estimates whose associated 95% credible interval does not include the null value of 1 for odds ratios). Placebo/no treatment was used as our control treatment for all analyses. As noted earlier, forest plots and league tables are provided to summarize all comparisons between the interventions studied.

Model Fit, Evaluation of Heterogeneity, and Evaluation of Inconsistency

As noted earlier, both fixed and random effects network meta-analyses were fit for all of our outcomes. Random effects models were planned to be our focus unless statistical criteria suggested fixed effects models were more appropriate. In all cases we found random effects to be preferred; **Appendix 4** provides a complete summary of model fit statistics, and these are not further discussed in the main text of the report.

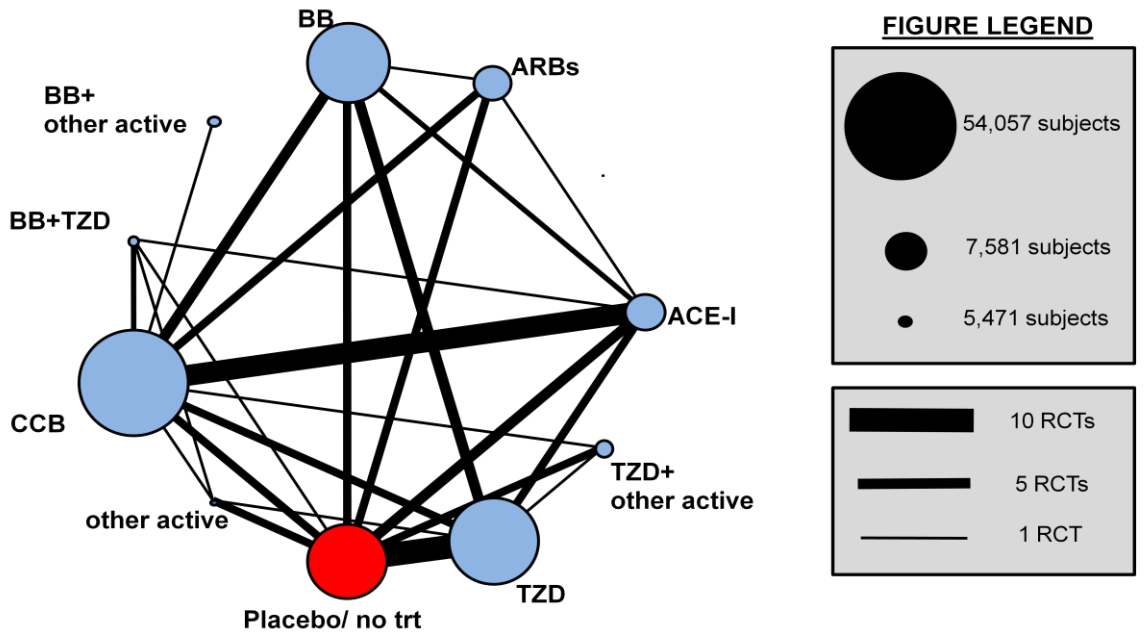
As described in Section 3.8 above, we planned extensive a priori sensitivity analyses addressing both clinical heterogeneity (i.e. patient age, gender, co-medications and so forth) and methodologic heterogeneity (i.e. risk of bias and presence of industry funding). We have provided extensive documentation of findings from these analyses in **Appendix 5** to provide readers the opportunity to review these findings. In practice we found that these statistical adjustments were not associated with notable changes in the summary estimates derived from our primary unadjusted network meta-analyses, and thus they are not commented on in the main text of the report. Modifications considered in analyses where the network geometry was restructured also did not lead to material changes in interpretation, and thus these are also not discussed in the review. In general the majority of our included studies were included in moderate to high risk patients, and thus analyses in lower risk patients typically did not include data on all of our therapies. We have thus focused our main text on results across populations, and have provided complete details on our sub-population analyses in our appendices.

Finally, our sensitivity analyses based on use of inconsistency models for network meta-analysis did not generate evidence to suggest any disagreements between direct and indirect evidence in our treatment networks. The relevant model fit information from these analyses is reported in **Appendix 4**. For brevity and given this finding, no further discussion of inconsistency is mentioned in the report's main text.

4.3.2.1 Findings, Overall Mortality

Figure 2 presents a network diagram summarizing pairwise comparisons that were available within our included RCTs. A total of 10 interventions were associated with RCTs that reported data on overall mortality amongst a total of 60 RCTs,[25,27-33,36-46,48-56,58-60,62,65,67,69,70,72,73,77,79-86,88-90,94,97,99,101,103,104,107,108,110,212] with the numbers of trials and randomized patients per treatment ranging between 1 - 28 and 837 – 54,057 (median 14,669), respectively. Comparisons between CCB with ACE-I and the control treatment with TZD were most common. Several comparisons of treatments were informed by single trials, and several comparisons have not been evaluated in head-to-head RCTs. The number of randomized participants was smaller for combination therapies assessed.

Figure 2:
Network Diagram, Overall Mortality (60 studies; 214,729 subjects; 15,575 events)



Joining lines indicate where head-to-head RCTs between interventions were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention.

Figure 3a provides a summary of the odds ratios against the control treatment, while **Figure 3b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 3a: Forest Plot of Comparisons versus the Control Treatment, Overall Mortality – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	0.98 (0.90 – 1.08)	2,708 / 39,616
TZD	0.91 (0.84 – 0.99)	2,580 / 37,615
ACE-I	0.93 (0.83 - 1.03)	677 / 7,581
CCB	0.91 (0.83 – 0.98)	4,374 / 54,057
ARBs	0.90 (0.81 – 1.00)	1,783 / 20,309
BB+TZD	0.88 (0.74 - 1.02)	452 / 2,776
TZD+other active	0.73 (0.61 - 0.89)	278 / 9,028
BB+other active	0.88 (0.71 – 1.12)	228 / 5,471
Other	0.97 (0.55 – 1.73)	25 / 836

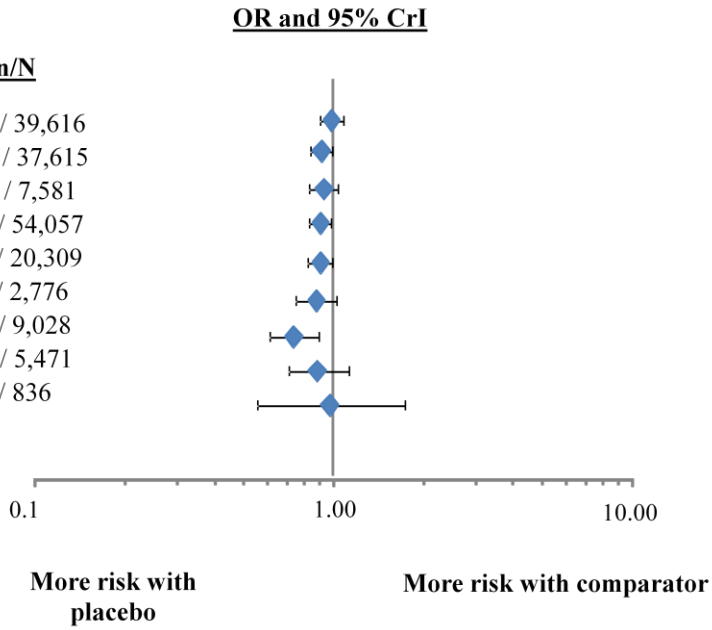


Figure 3b: League Table of all Pairwise Comparisons, Overall Mortality – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	BB	TZD	ACE-I	CCB	ARB	BB+TZD	TZD+other	BB+other	Other
0.99 (0.90 - 1.08)									
0.91 (0.84 - 0.99)	0.93 (0.84 - 1.01)								
0.93 (0.83 - 1.03)	0.94 (0.84 - 1.05)	1.02 (0.92 - 1.12)							
0.91 (0.83 - 0.98)	***0.92 (0.85 - 0.99)***	0.99 (0.91 - 1.08)	0.97 (0.89 - 1.08)						
0.90 (0.82 – 1.00)	0.92 (0.83 - 1.01)	0.99 (0.88 - 1.11)	0.97 (0.86 - 1.11)	1.00 (0.91 - 1.10)					
0.88 (0.74 - 1.02)	0.89 (0.75 - 1.04)	0.96 (0.82 - 1.12)	0.94 (0.81 - 1.10)	0.97 (0.83 - 1.12)	0.97 (0.81 - 1.15)				
0.73 (0.61 - 0.89)	***0.74 (0.61 - 0.90)***	***0.80 (0.66 - 0.97)***	***0.79 (0.65 - 0.97)***	***0.81 (0.67 - 0.98)***	***0.81 (0.67 - 0.99)***	0.84 (0.66 - 1.06)			
0.88 (0.71 - 1.12)	0.89 (0.72 - 1.14)	0.97 (0.77 - 1.22)	0.95 (0.76 - 1.22)	0.98 (0.79 - 1.22)	0.97 (0.78 - 1.25)	1.01 (0.78 - 1.32)	1.21 (0.91 - 1.62)		
0.97 (0.55 - 1.73)	0.99 (0.56 - 1.75)	1.06 (0.61 - 1.91)	1.05 (0.6 - 1.88)	1.08 (0.61 - 1.92)	1.08 (0.61 - 1.94)	1.11 (0.63 – 2.00)	1.34 (0.73 - 2.41)	1.11 (0.6 - 2.05)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the table; a value <1 suggests fewer deaths with the comparator than with the reference group. Statistically significant differences are bolded, underlined, italicized and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 3a)***. All summary odds ratios were associated with summary estimates suggestive of a reduced risk of death, while summary estimates for four (TZD, CCB, ARB, TZD+other active agents) showed statistically significant benefits (corresponding range of ORs from 0.73-0.91); the strongest effect was associated with TZD+other active treatments.

- ***Comparisons between active interventions (Figure 3b)***. The combination grouping of TZD + other active agents showed a statistically significant mortality reduction compared to BB, TZD, ACE-I, CCB and ARB (range of ORs 0.74-0.81); point estimates also suggested benefits compared to each of the competing combination therapy groupings, however these estimates were associated with wide 95% credible intervals that overlapped 1. CCB was associated with a mortality reduction compared to BB, and all other pairwise comparisons were associated with credible intervals that overlapped 1.

Table 5:
Summary of SUCRA and median ranks, overall mortality

Treatment	SUCRA (%)	Median rank (95% CrI)
TZD+other	0.96	1 (1 - 4)
BB+TZD	0.65	3 (1 - 9)
BB+other	0.59	4 (1 - 10)
CCB	0.57	5 (2 - 8)
ARB	0.56	5 (2 - 8)
TZD	0.53	5 (2 - 8)
ACE-I	0.43	6 (3 - 9)
Other	0.39	8 (1 - 10)
BB	0.18	9 (6 - 10)
PL/no trt	0.13	9 (6 - 10)

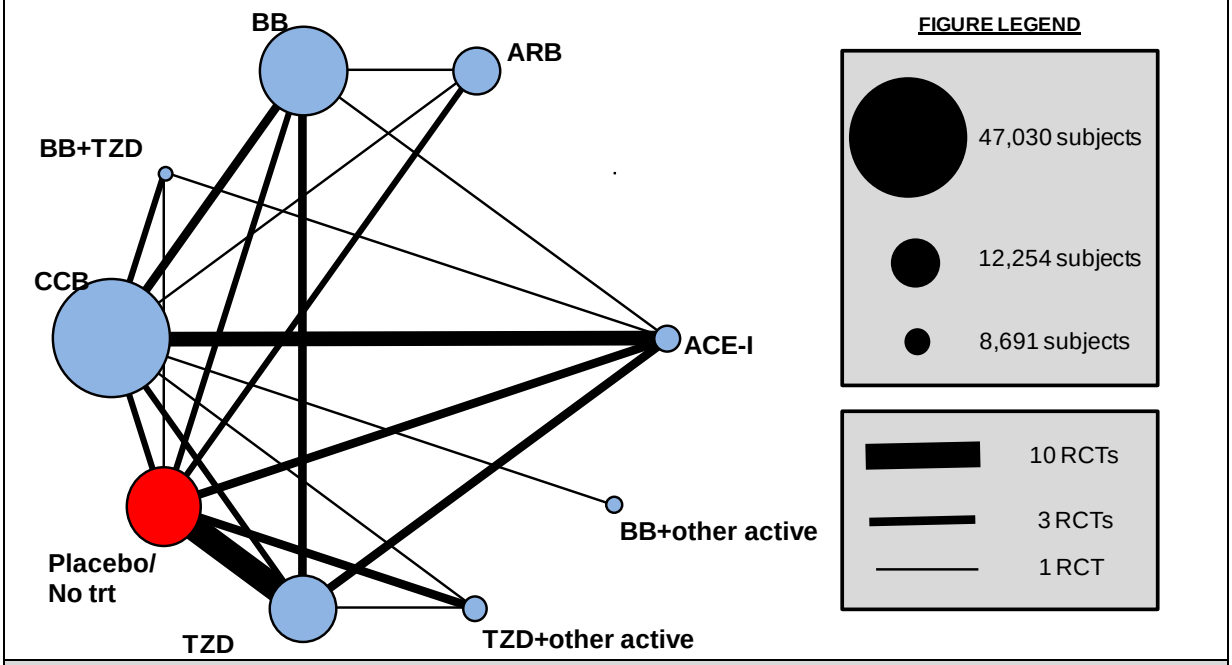
Treatments are ordered from highest to lowest SUCRA (higher values are better). Median ranks with credible intervals are shown; ranks nearer 1 are better. Wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the least mortality, second least mortality, and so forth is provided in **Table 5**. Findings were supportive of results observed from the comparisons summarized above. TZD+other active treatments were associated with the most favorable SUCRA value and median treatment rank, while the control treatment demonstrated the lowest for both. Combination therapies other than TZD+other active therapies were comparable to CCB, ARB, TZD and ACE-I.

4.3.2.2 Findings, Cardiovascular Mortality

Figure 4 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 9 interventions were associated with RCTs that reported data on cardiovascular mortality across 39 RCTs,[25,27-30,33,36,37,39-46,48,50,52-57,59-62,65-67,69,73,80,84,88,92,101,103,108] with the numbers of trials and randomized patients per treatment ranging from 1-20 and 2,726 – 47,030 (median 19,632), respectively. Comparisons of TZD with placebo/no treatment and CCB with ACE-I were most prevalent. Several comparisons of treatments were informed by single trials, and several comparisons have not been evaluated in head-to-head RCTs. The numbers of studied patients on combination therapies was again proportionately smaller.

Figure 4: Network Diagram, Cardiovascular Mortality (39 studies; 173, 455 subjects; 6,495 events)



Joining lines indicate where head-to-head RCTs between interventions were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention.

Figure 5a provides a summary of the odds ratios against the control treatment, while **Figure 5b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 5a: Forest Plot of Comparisons versus the Control Treatment, Cardiovascular Mortality – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	0.97 (0.83 - 1.12)	1,212 / 32,109
TZDs	0.87 (0.77 – 1.00)	689 / 22,703
ARBs	0.92 (0.78 - 1.08)	781 / 19,362
ACE-I	0.90 (0.73 - 1.11)	357 / 7,373
CCB	0.87 (0.75 – 1.00)	1,628 / 47,030
BB+TZD	0.81 (0.62 - 1.03)	266 / 2,776
BB+other active	0.75 (0.53 - 1.07)	115 / 5,471
TZD+other active	0.65 (0.51 - 0.81)	201 / 8,681

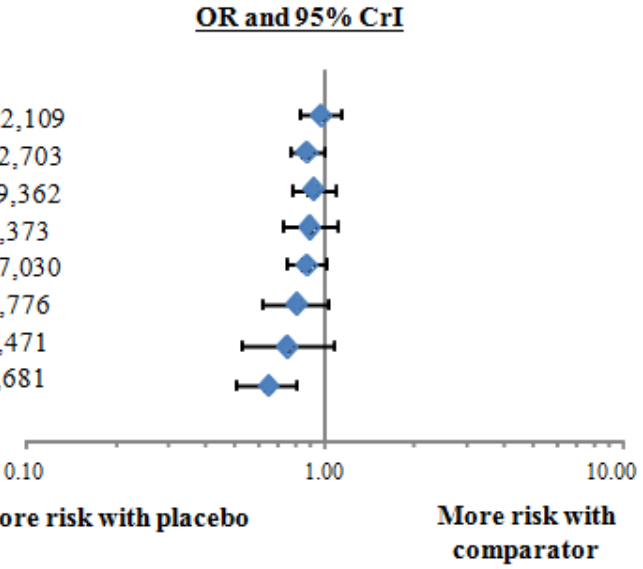


Figure 5b: League Table of all Pairwise Comparisons, Cardiovascular Mortality – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	BB	TZD	ARB	ACE-I	CCB	BB+TZD	BB+other	TZD+other
0.97 (0.83 - 1.12)								
0.87 (0.77 – 1.00)	0.90 (0.76 - 1.07)							
0.92 (0.78 - 1.08)	0.94 (0.80 - 1.13)	1.05 (0.87 - 1.28)						
0.90 (0.73 - 1.11)	0.92 (0.74 - 1.15)	1.03 (0.83 - 1.27)	0.98 (0.76 - 1.24)					
0.87 (0.75 – 1.00)	0.90 (0.78 - 1.03)	1.00 (0.84 - 1.18)	0.95 (0.80 - 1.12)	0.97 (0.79 - 1.19)				
0.81 (0.62 - 1.03)	0.83 (0.64 - 1.07)	0.93 (0.70 - 1.19)	0.88 (0.66 - 1.15)	0.90 (0.69 - 1.14)	0.93 (0.73 - 1.16)			
0.75 (0.53 - 1.07)	0.77 (0.55 - 1.11)	0.86 (0.60 - 1.24)	0.82 (0.57 - 1.18)	0.84 (0.57 - 1.23)	0.86 (0.63 - 1.19)	0.93 (0.64 - 1.41)		
0.65 (0.51 - 0.81)	***0.67 (0.52 - 0.86)***	***0.74 (0.58 - 0.93)***	***0.71 (0.54 - 0.92)***	***0.72 (0.54 - 0.96)***	***0.74 (0.58 - 0.94)***	0.80 (0.58 - 1.11)	0.86 (0.57 - 1.28)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the step-ladder; a value <1 suggests fewer deaths with the comparator than with the reference group. Statistically significant differences are bolded, underlined, italicized and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 5a)***. Each of TZD, CCB, and TZD+other active treatments were associated with statistically significant reductions in the risk of cardiovascular death (range of ORs 0.65-0.87), the strongest of which was associated with TZD+other active treatments; the other interventions were also associated with benefits based on their point estimates, however their associated 95% credible intervals also included the null value of 1. BB+TZD also approached statistical significance with a 95% credible interval which neared exclusion of the null value of 1.

- ***Comparisons between active interventions (Figure 5b)***. The combination grouping of TZD + other active agents was found to demonstrate a statistically significant reduction in cardiovascular mortality compared to each monotherapy (BB, TZD, ARB, ACE-I, and CCB; range of ORs 0.65-0.74); point estimates for this intervention also suggested benefits compared to the competing combination therapy groupings, however these estimates were more uncertain and credible intervals did not exclude a possible null difference. All other pairwise comparisons involving the remaining interventions were associated with credible intervals that overlapped 1.

Table 6:
Summary of SUCRA and median ranks, cardiovascular mortality

Treatment	SUCRA (%)	Median rank (95% CrI)
TZD+other	0.96	1 (1 - 3)
BB+other	0.75	2 (1 - 9)
BB+TZD	0.68	3 (1 - 8)
CCB	0.53	5 (3 - 7)
TZDs	0.52	5 (2 - 8)
ACE-I	0.42	6 (2 - 9)
ARB	0.36	6 (3 - 9)
BB	0.17	8 (4 - 9)
PL/no trt	0.10	8 (6 - 9)

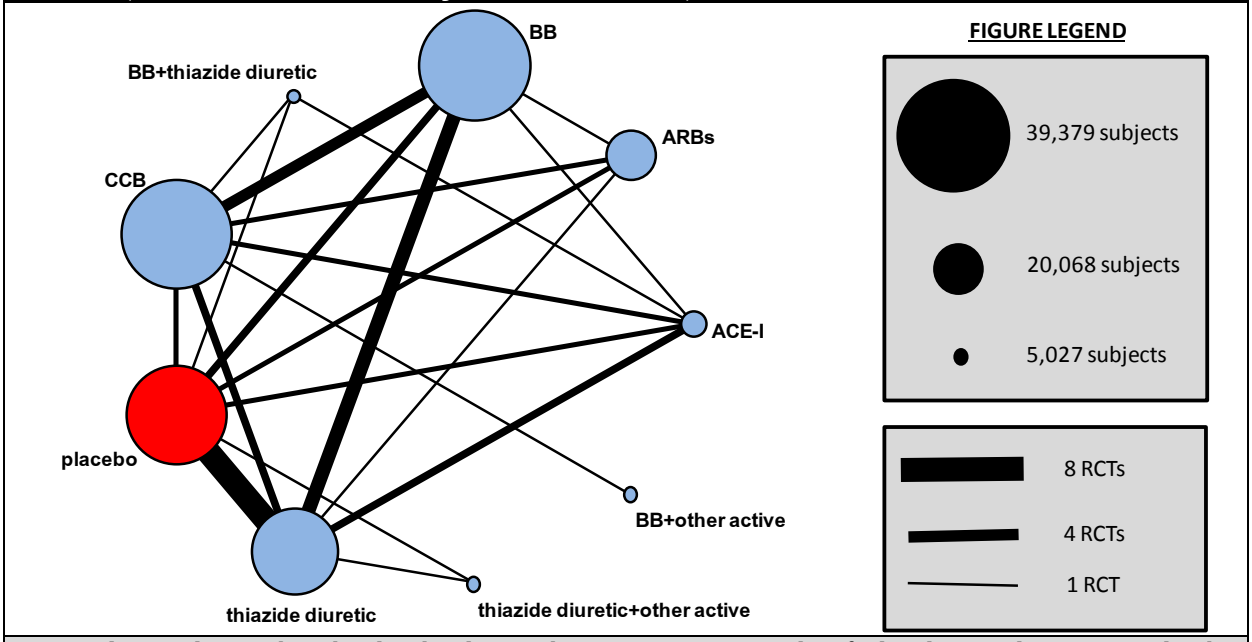
Treatments are ordered from highest to lowest SUCRA value (higher values are better). Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the least cardiovascular mortality, second least cardiovascular mortality, and so forth is provided in **Table 6**. Findings were supportive of results observed from the corresponding pairwise comparisons discussed above; TZD+other active treatments was associated with the most favorable SUCRA value and median treatment rank, while the control treatment of placebo/no treatment demonstrated the lowest for both. The credible interval surrounding the median rank for TZD+other was much narrower than seen for all other interventions. Combination therapies other than TZD+other active therapies were also increased relative to all monotherapies.

4.3.2.3 Findings, Stroke

Figure 6 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 9 interventions were associated with RCTs that reported data on stroke across 37 RCTs,[25,27-30,32-34,36,37,40,42-46,48-50,52,53,55,56,58,59,62,65-69,71,81,84,88,98,99] with the numbers of trials and randomized patients per treatment ranging from 1 - 19 and 2,632 – 39,380 (median 20,069), respectively. Comparisons between placebo/no treatment with TZD, BB with TZD, ACE-I with TZD and CCB with BB were most prevalent. Many comparisons of treatments were informed by single trials, and many comparisons have not been evaluated in head-to-head RCTs. The numbers of studied patients on combination therapies was again proportionately smaller.

Figure 6: Network Diagram, Stroke (37 studies, 190,903 subjects, 6,982 events)



Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Figure 7a provides a summary of the odds ratios against the control treatment, while **Figure 7b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 7a: Forest Plot of Comparisons versus the Control Treatment, Stroke – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	0.86 (0.68 - 1.07)	1,205 / 39,380
TZD	0.67 (0.54 - 0.81)	870 / 29,081
ACE-I	0.85 (0.62 - 1.11)	593 / 7,791
CCB	0.68 (0.54 - 0.84)	1,397 / 44,447
ARBs	0.72 (0.54 - 0.94)	781 / 20,069
BB+TZD	0.76 (0.50 - 1.12)	260 / 2,632
TZD+other active	0.41 (0.25 - 0.66)	182 / 5,027
BB+other active	0.83 (0.47 - 1.45)	196 / 5,471

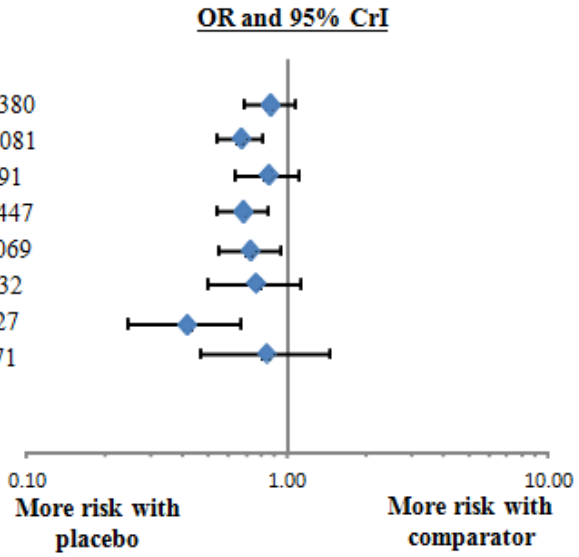


Figure 7b: League Table of all Pairwise Comparisons, Stroke – Summary Odds Ratios and Credible Intervals

PL/ NO TRT							
0.86 (0.68 - 1.07)	**BB**						
0.67 (0.54 - 0.81)	***0.77 (0.61 - 0.99)***	**TZD**					
0.85 (0.62 - 1.11)	0.99 (0.71 - 1.34)	1.27 (0.94 - 1.70)	**ACE-I**				
0.68 (0.54 - 0.84)	***0.79 (0.63 - 0.99)***	1.02 (0.80 - 1.31)	0.80 (0.60 - 1.09)	**CCB**			
0.72 (0.54 - 0.94)	0.84 (0.63 - 1.13)	1.08 (0.79 - 1.49)	0.85 (0.60 - 1.25)	1.06 (0.81 - 1.42)	**ARB**		
0.76 (0.50 - 1.12)	0.89 (0.57 - 1.35)	1.15 (0.74 - 1.73)	0.90 (0.59 - 1.36)	1.13 (0.74 - 1.67)	1.06 (0.65 - 1.66)	**BB+TZD**	
0.41 (0.25 - 0.66)	***0.48 (0.28 - 0.79)***	***0.62 (0.39 - 0.97)***	***0.49 (0.28 - 0.83)***	***0.61 (0.36 – 1.00)***	***0.58 (0.32 - 0.97)***	***0.54 (0.29 – 1.00)***	**TZD+ other**
0.83 (0.47 - 1.45)	0.97 (0.55 - 1.70)	1.25 (0.70 - 2.22)	0.98 (0.54 - 1.80)	1.23 (0.73 - 2.06)	1.16 (0.63 - 2.07)	1.09 (0.57 - 2.13)	2.01 (0.99 - 4.25) **BB+other**

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the step-ladder; a value <1 suggests fewer strokes with the comparator than with the reference group. Statistically significant differences are bolded, underlined, italicized and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 7a)***. Each of TZD, CCB, ARB, and TZD+other active treatments were associated with statistically significant reductions in the risk of stroke compared to the reference treatment (range of ORs 0.41-0.72), the strongest effect being associated with TZD+other active treatments. All remaining treatments were associated with point estimates which also suggested a benefit compared to the control treatment, however their 95% credible intervals included the null value of 1.

- ***Comparisons between active agents (Figure 7b)***. TZD+other active agents demonstrated a statstically significant reduction in the risk of stroke compared to all other active regimens (range of ORs 0.41-0.62). BB exhibited a statistically significantly increased risk compared to both TZD and CCB. All other comparisons between active treatments were associated with 95% credible intervals that included the null value of 1.

Table 7:
Summary of SUCRA and median ranks, stroke

Treatment	SUCRA (%)	Median rank (95% CrI)
TZD+other	0.98	1 (1 - 3)
TZD	0.72	3 (2 - 6)
CCB	0.70	3 (2 - 6)
ARB	0.58	4 (2 - 8)
BB+TZD	0.49	5 (2 - 9)
BB+other	0.37	6 (2 - 9)
ACE-I	0.31	7 (3 - 9)
BB	0.28	7 (4 - 9)
PL/no trt	0.07	9 (7 - 9)

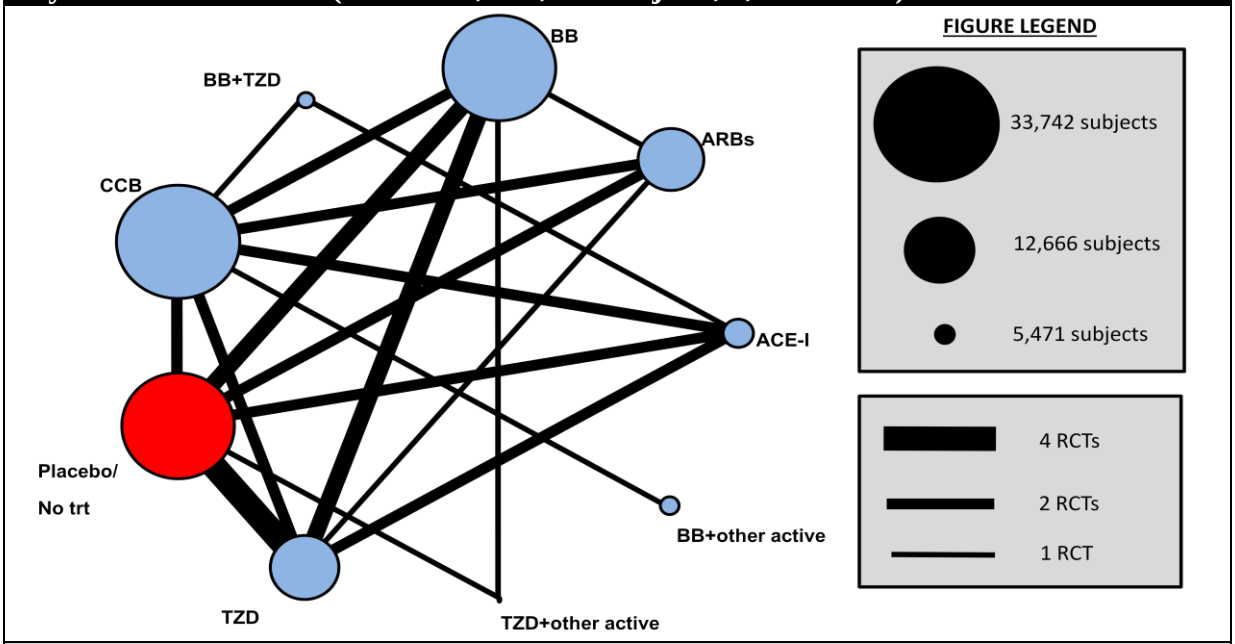
Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest strokes, second fewest strokes and so forth is provided in **Table 7**. Findings were supportive of results observed from the corresponding pairwise comparisons discussed above; TZD+other active treatments were associated with the most favorable SUCRA value and median treatment rank, while the reference treatment demonstrated the lowest for both.

4.3.2.4 Findings, Myocardial Infarction

Figure 8 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 9 interventions were associated with RCTs that reported data on MI across 27 RCTs,[25,28,32,33,38,42,45,46,49,50,52,53,55,56,58,66,67,69,71,80,81,84,87,88,92,99,106] with the numbers of trials and randomized patients per treatment ranging from 1 - 12 and 559 – 34,742 (median 12,657), respectively. Comparisons between the control treatment with TZD were most prevalent (four studies), while several comparisons were informed by two studies. Several comparisons of treatments were informed by single trials, and several comparisons have not been evaluated in head-to-head RCTs.

Figure 8: Network Diagram,
Myocardial Infarction (27 studies, 132,803 subjects, 4,933 events)



Joining lines indicate where head-to-head RCTs between interventions were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention.

Figure 9a provides a summary of the odds ratios against the control treatment, while **Figure 9b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 9a: Forest Plot of Comparisons versus the Control Treatment, Myocardial Infarction – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	0.94 (0.74 - 1.20)	1,069 / 25,945
TZDs	0.76 (0.57 – 0.99)	271 / 12,657
CCB	0.89 (0.68 - 1.12)	1,362 / 34,742
ARBs	1.05 (0.77 - 1.41)	580 / 12,986
ACE-I	0.66 (0.48 – 0.91)	239 / 6,395
BB+TZD	0.74 (0.45 - 1.21)	154 / 2,213
BB+other active	0.75 (0.43 – 1.28)	157 / 5,471
TZD+other active	0.98 (0.29 - 3.22)	6 / 559

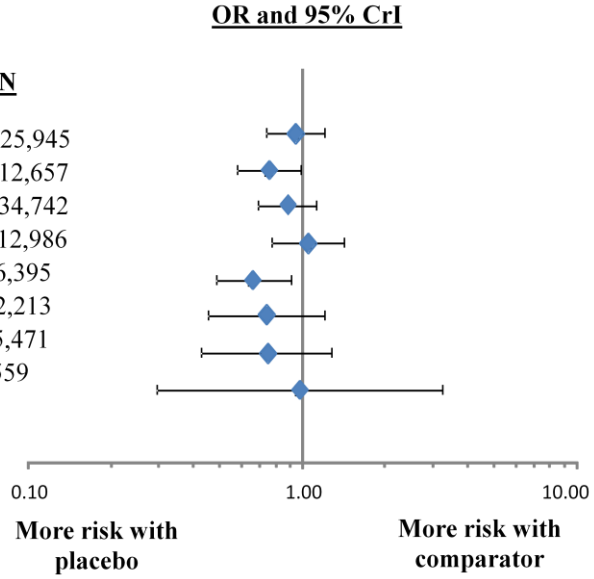


Figure 9b: League Table of all Pairwise Comparisons, Myocardial Infarction – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	BB	TZD	CCB	ARB	ACE-I	BB+TZD	BB+other	TZD+ other
0.94 (0.74 - 1.20)								
0.76 (0.57 - 0.99)	0.80 (0.61 - 1.07)							
0.89 (0.68 - 1.12)	0.94 (0.72 - 1.21)	1.17 (0.86 - 1.57)						
1.05 (0.77 - 1.41)	1.11 (0.78 - 1.59)	1.39 (0.95 - 2.03)	1.18 (0.87 - 1.64)					
0.66 (0.48 - 0.91)	***0.70 (0.52 - 0.95)***	0.87 (0.63 - 1.21)	0.74 (0.56 - 1.01)	***0.63 (0.42 - 0.95)***				
0.74 (0.45 - 1.21)	0.78 (0.48 - 1.28)	0.98 (0.58 - 1.63)	0.83 (0.53 - 1.32)	0.70 (0.41 - 1.21)	1.12 (0.7 - 1.77)			
0.75 (0.43 - 1.28)	0.80 (0.45 - 1.37)	0.99 (0.55 - 1.74)	0.85 (0.52 - 1.37)	0.71 (0.39 - 1.27)	1.14 (0.63 - 1.99)	1.01 (0.51 - 1.95)		
0.98 (0.29 - 3.22)	1.04 (0.31 - 3.46)	1.29 (0.38 - 4.36)	1.11 (0.33 - 3.71)	0.93 (0.27 - 3.18)	1.48 (0.43 - 5.03)	1.32 (0.37 - 4.74)	1.31 (0.36 - 4.81)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the step-ladder; a value <1 suggests fewer MIs with the comparator than with the reference group. Statistically significant differences are bolded, underlined, italicized and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 9a)***. Amongst all interventions, only TZD (OR 0.76) and ACE-I (OR 0.66) were associated with statistically significant reductions of MI. Near all other interventions (except ARBs) were associated with point estimates suggesting a reduction in the risk of MI, however all corresponding 95% credible intervals for these comparisons included 1.

- ***Comparisons between active agents (Figure 9b)***. Credible intervals for the majority of comparisons between interventions included 1, suggesting insufficient evidence of a difference between the active treatments. ACE-I were found to be associated with a statistically significantly reduced risk compared to BB and ARB. The lower bound of the 95% credible interval for the estimate comparing TZD with ARB suggests there may also be a reduced risk with TZD relative to ARB.

Table 8:
Summary of SUCRA and median ranks, MI

Treatment	SUCRA (%)	Median rank (95% CrI)
ACE-I	0.86	2 (1 - 5)
TZD	0.69	3 (1 - 7)
BB+TZD	0.69	3 (1 - 9)
BB+other	0.67	3 (1 - 9)
CCB	0.45	5 (3 - 8)
TZD+other	0.40	7 (1 - 9)
BB	0.34	6 (3 - 9)
PL/no trt	0.23	7 (4 - 9)
ARB	0.19	8 (4 - 9)

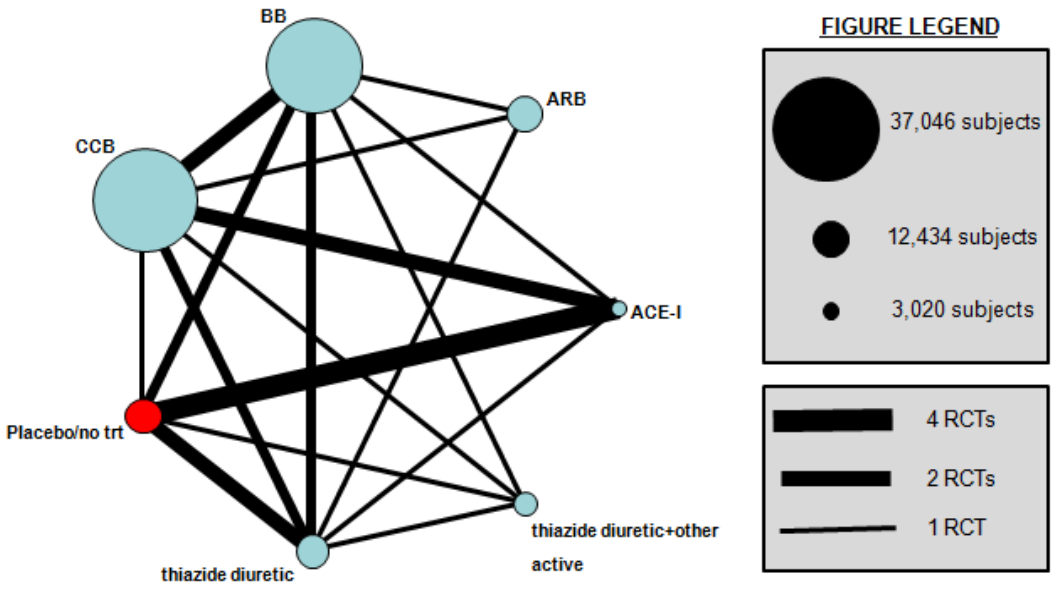
Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest MIs, second fewest MIs, and so forth is provided in **Table 8**. Findings were supportive of results observed from the corresponding pairwise comparisons discussed above; ACE-I were associated with the most favorable SUCRA value and median treatment rank. Monotherapy with TZD and the combination therapies BB+TZD and BB+other active treatments produced similar SUCRAs and median rankings. The reference treatment and ARB were associated with the least supportive values for both parameters.

4.3.2.5 Findings, Incident Cancers

Figure 10 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 8 interventions were associated with RCTs that reported data on incident cancers across 25 RCTs, [25,27,30,32,34,36,44-46,53,54,56-58,65,66,69-72,78,85,87,98,106] with the numbers of trials and randomized patients per treatment ranging from 1-4 and 2,632 – 37,046 (median 10,641), respectively. Comparisons between the reference treatment with ACE-I and CCB with BB were most prevalent. Many comparisons of treatments were informed by single trials, and several comparisons have not been evaluated in head-to-head RCTs.

Figure 10:
Network Diagram, Incident Cancers (25 studies, 114,472 subjects, 5,737 events)



Joining lines indicate where head-to-head RCTs between interventions were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention.

Figure 11a provides a summary of the odds ratios against the control treatment, while **Figure 11b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 11a: Forest Plot of Comparisons versus the Control Treatment, Incident Cancers – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	1.00 (0.80 - 1.26)	1,549 / 29,996
ARB	0.88 (0.67 - 1.15)	826 / 12,434
ACE-I	1.12 (0.80 - 1.55)	230 / 3,025
TZDs	1.05 (0.84 - 1.32)	218 / 9,875
CCB	1.03 (0.82 - 1.28)	2,196 / 37,047
BB+TZD	1.05 (0.77 – 1.43)	229 / 2,632
TZD+other active	0.81 (0.60 - 1.12)	166 / 8,056

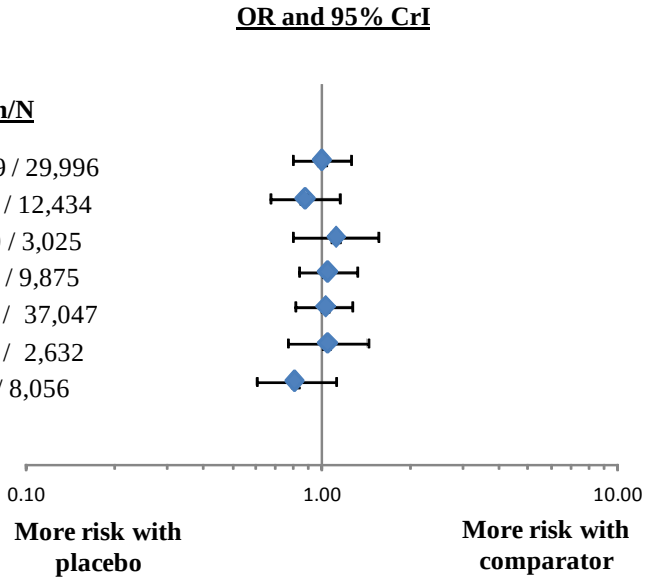


Figure 11b: League Table of all Pairwise Comparisons, Incident Cancers – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	BB	ARB	ACE-I	TZD	CCB	BB+TZD	TZD+other
1.00 (0.80 - 1.26)							
0.88 (0.67 - 1.15)	0.88 (0.72 - 1.05)						
1.12 (0.80 - 1.55)	1.11 (0.84 - 1.51)	1.27 (0.94 - 1.77)					
1.05 (0.84 - 1.32)	1.04 (0.81 - 1.36)	1.2 (0.89 - 1.60)	0.94 (0.64 - 1.34)				
1.03 (0.82 - 1.28)	1.03 (0.88 - 1.16)	1.18 (0.97 - 1.40)	0.92 (0.69 - 1.18)	0.98 (0.76 - 1.26)			
1.05 (0.77 - 1.43)	1.04 (0.79 - 1.39)	1.19 (0.88 - 1.64)	0.93 (0.72 - 1.22)	1.00 (0.70 - 1.41)	1.01 (0.80 - 1.33)		
0.81 (0.60 - 1.12)	0.81 (0.60 - 1.08)	0.93 (0.67 - 1.27)	0.73 (0.50 - 1.05)	0.78 (0.58 - 1.04)	0.79 (0.61 - 1.04)	0.78 (0.53 - 1.12)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of cancer with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 11a)***. All comparisons against the control treatment were associated with 95% credible intervals that could not rule out a possible null difference. No statistically significant differences were observed.
- ***Comparisons between active agents (Figure 11b)***. Similar to comparisons of the active interventions against the control treatment, all comparisons between active therapies were associated with 95% credible intervals that included 1 and thus did not suggest any statistically significantly increased risks of cancers with any particular regimen.

Table 9:
Summary of SUCRA and median ranks, cancers

Treatment	SUCRA (%)	Median rank (95% CrI)
TZD+other	0.90	1 (1 - 6)
ARB	0.83	2 (1 - 6)
PL/no trt	0.49	4 (1 - 8)
BB	0.48	5 (2 - 8)
CCB	0.38	5 (3 - 8)
BB+TZD	0.37	6 (1 - 8)
TZD	0.35	6 (2 - 8)
ACE-I	0.21	7 (2 - 8)

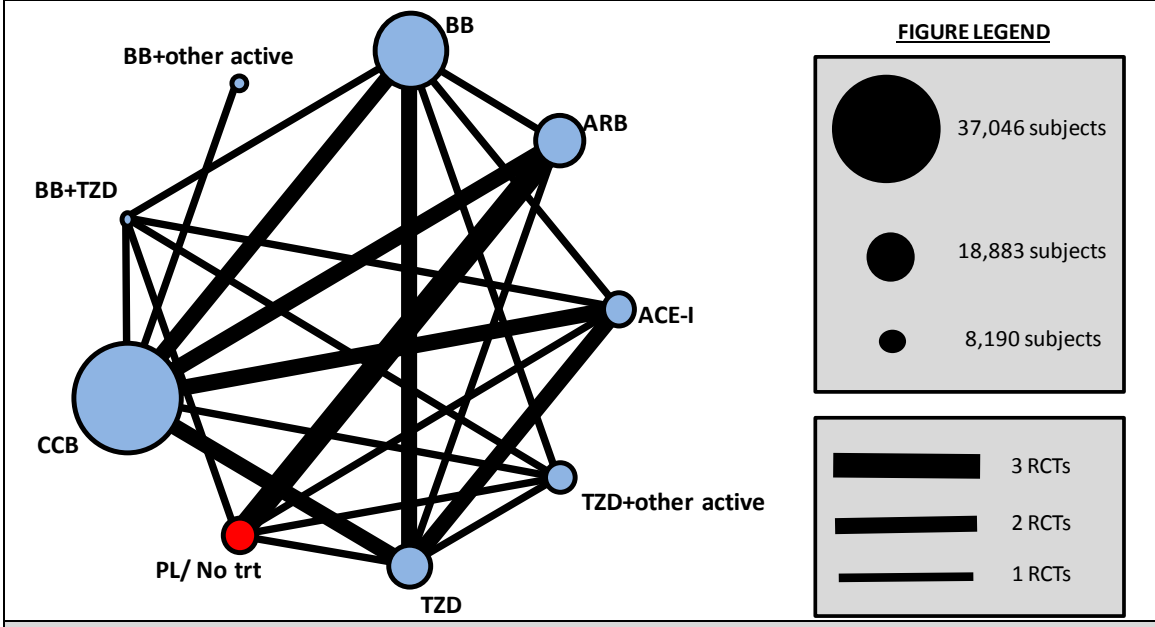
Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest incident cancers, second fewest cancers and so forth is provided in **Table 9**. TZD+other active treatments was associated with the most favorable SUCRA value and median treatment rank, followed by ARB; this is in agreement with the finding of both treatments' comparisons against the control treatment lying below 1. Despite the increased SUCRA value for these interventions, interpretation of findings for this outcome should be focused on the current lack of statistically significant differences between therapies.

4.3.2.6 Findings, Incident Diabetes

Figure 12 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 9 interventions were associated with RCTs that reported data on incident diabetes across 25 RCTs, [27,29-31,36,43-46,50,51,53-57,63-65,67,71,81,88,105,111] with the numbers of trials and randomized patients per treatment ranging from 1 - 9 and 2,490 – 38,722 (median 13,217), respectively. Comparisons between the reference treatment with ARBs were most prevalent. Several comparisons of treatments were informed by single trials, and several comparisons have not been evaluated in head-to-head RCTs.

Figure 12: Network Diagram,
Incident Diabetes (25 studies, 139,608 subjects, 12,542 events)



Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Figure 13a provides a summary of the odds ratios against the control treatment, while **Figure 13b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 13a: Forest Plot of Comparisons versus the Control Treatment, Incident Diabetes – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
TZD	1.55 (1.16 - 2.11)	1,060 / 16,140
BB	1.25 (0.92 - 1.75)	1,942 / 28,785
CCB	1.07 (0.79 - 1.45)	2,906 / 38,722
ARB	0.84 (0.65 - 1.05)	2,954 / 18,813
ACE-I	0.85 (0.62 - 1.16)	462 / 7,983
BB+TZD	1.02 (0.64 - 1.67)	104 / 2,490
TZD+other active	1.58 (1.03 - 2.45)	378 / 8,190
BB+other active	1.24 (0.71 - 2.14)	251 / 5,186

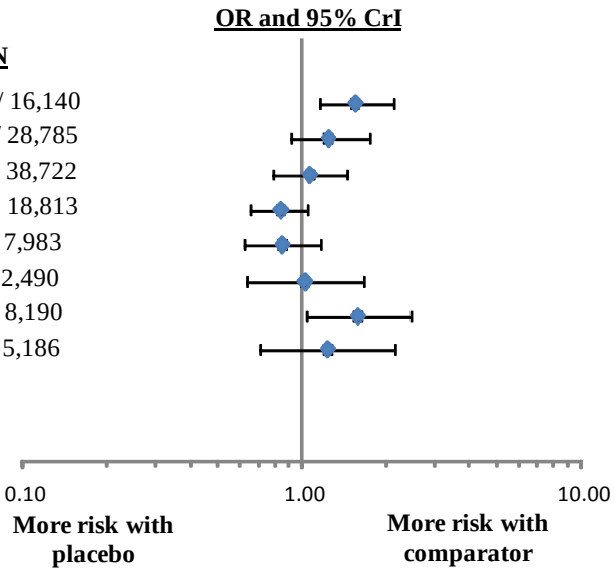


Figure 13b: League Table of all Pairwise Comparisons, Incident Diabetes – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	TZD	BB	CCB	ARB	ACE-I	BB+TZD	TZD+other	BB+other
1.55 (1.16 - 2.11)								
1.25 (0.92 - 1.75)	0.80 (0.61 - 1.08)							
1.07 (0.79 - 1.45)	***0.69 (0.52 - 0.89)***	0.86 (0.66 - 1.07)						
0.84 (0.65 - 1.05)	***0.54 (0.39 - 0.72)***	***0.67 (0.48 - 0.88)***	0.79 (0.59 - 1.02)					
0.85 (0.62 - 1.16)	***0.55 (0.42 - 0.71)***	***0.68 (0.50 - 0.91)***	0.79 (0.61 - 1.04)	1.01 (0.74 - 1.42)				
1.02 (0.64 - 1.67)	0.66 (0.41 - 1.05)	0.82 (0.51 - 1.31)	0.96 (0.63 - 1.49)	1.22 (0.77 - 2.02)	1.21 (0.78 - 1.88)			
1.58 (1.03 - 2.45)	1.02 (0.7 - 1.47)	1.27 (0.83 - 1.88)	***1.49 (1.03 - 2.14)***	***1.89 (1.25 - 2.95)***	***1.87 (1.23 - 2.82)***	1.55 (0.89 - 2.63)		
1.24 (0.71 - 2.14)	0.79 (0.46 - 1.35)	0.99 (0.58 - 1.64)	1.16 (0.72 - 1.83)	1.47 (0.86 - 2.54)	1.46 (0.85 - 2.48)	1.21 (0.64 - 2.24)	0.78 (0.43 - 1.40)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the step-ladder; a value <1 suggests less incident diabetes with the comparator than with the reference group. Statistically significant differences are bolded, underlined, italicized and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 13a)***. Both monotherapy with TZD and combination therapy with TZD+other active agents were associated with a statistically significantly increased risk of diabetes compared to the reference treatment (range of ORs 1.55-1.58). BB, CCB, BB+TZD and BB+other active active agents were associated with point estimates suggesting more risk while those for ARB and ACE-I suggested reduced risk, however all of these comparisons had 95% credible intervals that included 1.
- ***Comparisons between active agents (Figure 13b)***. TZD were found to be associated with an increased risk compared to each of CCB, ARB, and ACE-I; the same was true for

TZD in combination with other active agents. BB was associated with an increased risk when compared to each of ARB and ACE-I.

Table 10:
Summary of SUCRA and median ranks, incident diabetes

Treatment	SUCRA (%)	Median rank (95% CrI)
ARB	0.90	2 (1 - 4)
ACE-I	0.87	2 (1 - 5)
PL/no trt	0.64	4 (2 - 7)
BB+TZD	0.62	4 (1 - 8)
CCB	0.56	5 (2 - 6)
BB+other	0.38	6 (1 - 9)
BB	0.33	6 (4 - 8)
TZD+other	0.11	8 (5 - 9)
TZD	0.10	8 (6 - 9)

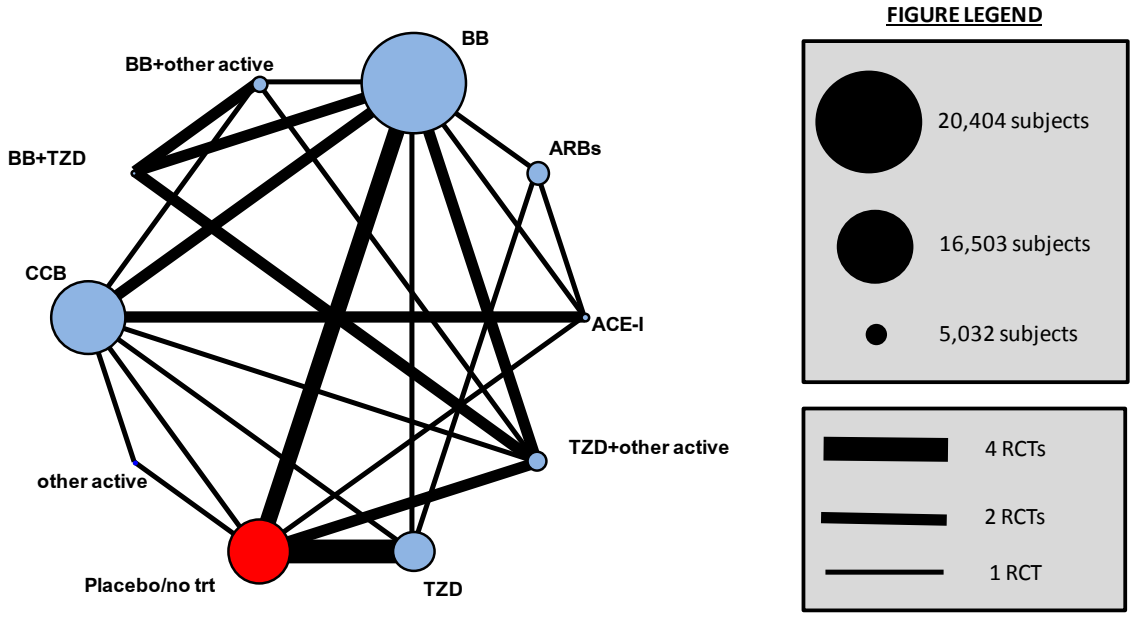
Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest incident cases of diabetes, second fewest incident cases of diabetes, and so forth is provided in **Table 10**. ARB and ACE-I were associated with the most favorable SUCRA value and median treatment rank, while TZD and TZD+other active treatments were associated with values reinforcing the increased risk of diabetes noted from pairwise comparisons derived in network meta-analyses summarized above.

4.3.2.7 Findings, Sexual Dysfunction

Figure 14 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 10 interventions were associated with RCTs that reported data on sexual dysfunction across 21 RCTs, [27,28,32,33,36,38,40,43,44,53-55,62,74,76,78,87,92,102,111,112] with the numbers of trials and randomized patients per treatment ranging from 1 - 10 and 120 – 20,404 (median 4,508), respectively. Comparisons between TZD with the control treatment and BB with the control treatment were most prevalent. Several comparisons of treatments were informed by single trials, and Several comparisons have not been evaluated in head-to-head RCTs. The sample size studied for several treatments was very small.

Figure 14:
Network Diagram, Sexual Dysfunction (21 studies, 67,634 subjects, 3,328 events)



Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Figure 15a provides a summary of the odds ratios against the control treatment, while **Figure 15b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 15a: Forest Plot of Comparisons versus the Control Treatment, Sexual Dysfunction – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
TZDs	2.79 (1.32 - 5.88)	240 / 6,188
BB	1.86 (0.96 - 3.59)	1,249 / 20,404
CCB	1.96 (0.91 - 4.29)	814 / 16,504
ARBs	1.38 (0.38 - 4.97)	167 / 5,033
ACE-I	1.60 (0.51 - 4.40)	133 / 817
BB+TZD	4.64 (1.08 - 19.78)	25 / 152
TZD+other active	2.65 (1.07 - 6.34)	164 / 3,983
BB+other active	3.16 (0.95 - 10.43)	211 / 2,741
Other	3.81 (0.89 - 16.69)	16 / 120

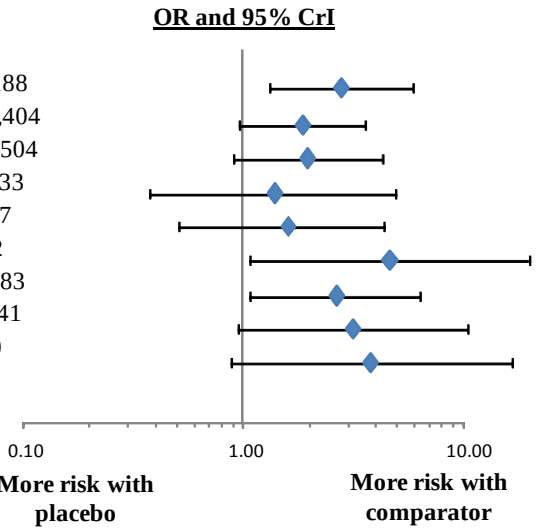


Figure 15b: League Table of all Pairwise Comparisons, Sexual Dysfunction – Summary Odds Ratios and Credible Intervals

PL/ NO TRT								
2.79 (1.32 - 5.88)	**TZD**							
1.86 (0.96 - 3.59)	0.67 (0.29 - 1.54)	**BB**						
1.96 (0.91 - 4.29)	0.70 (0.29 - 1.73)	1.05 (0.52 - 2.14)	**CCB**					
1.38 (0.38 - 4.97)	0.50 (0.13 - 1.93)	0.74 (0.23 - 2.35)	0.70 (0.19 - 2.56)	**ARB**				
1.60 (0.51 - 4.40)	0.57 (0.17 - 1.80)	0.86 (0.3 - 2.21)	0.81 (0.27 - 2.14)	1.16 (0.28 - 4.22)	**ACE-I**			
4.64 (1.08 - 19.78)	1.67 (0.35 - 7.74)	2.49 (0.62 - 9.88)	2.37 (0.56 - 9.66)	3.35 (0.57 - 19.73)	2.91 (0.59 - 15.87)	**BB+TZD**		
2.65 (1.07 - 6.34)	0.95 (0.32 - 2.73)	1.42 (0.57 - 3.39)	1.35 (0.54 - 3.22)	1.92 (0.46 - 7.86)	1.66 (0.51 - 5.82)	0.57 (0.14 - 2.30)	**TZD+Other**	
3.16 (0.95 - 10.43)	1.13 (0.31 - 4.12)	1.70 (0.55 - 5.19)	1.62 (0.55 - 4.67)	2.29 (0.47 - 11.04)	1.98 (0.51 - 8.41)	0.68 (0.16 - 2.91)	1.20 (0.37 - 3.94)	**BB+Other**
3.81 (0.89 - 16.69)	1.36 (0.28 - 6.76)	2.04 (0.45 - 9.41)	1.94 (0.45 - 8.38)	2.75 (0.43 - 18.16)	2.39 (0.45 - 14.15)	0.82 (0.12 - 6.02)	1.43 (0.29 - 7.35)	1.20 (0.21 - 7.04)	**Other**

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests less sexual dysfunction with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow.

- ***Comparisons with the control treatment (Figure 15a)***. All interventions involving a thiazide diuretic (TZD monotherapy, BB+TZD, TZD+other active agents) were all associated with statistically significantly increased likelihoods of sexual dysfunction compared to the control treatment (range of ORs 2.65-4.64). All agents were associated with summary estimates suggesting an increased risk; however all comparisons were generally associated with wide 95% credible intervals, and those for other regimens overlapped the null value of 1.

- ***Comparisons between active interventions (Figure 15b)***. No statistically significant increases in the risk of sexual dysfunction were identified when comparing the different active interventions. A limitation of these findings is the very wide credible intervals associated with virtually all comparisons in the network of treatments.

Table 11:
Summary of SUCRA and median ranks, sexual dysfunction

Treatment	SUCRA (%)	Median rank (95% CrI)
PL/no trt	0.93	1 (1 - 4)
ARB	0.74	3 (1 - 9)
ACE-I	0.68	3 (1 - 9)
BB	0.61	4 (2 - 8)
CCB	0.58	5 (2 - 8)
TZD+other	0.39	7 (2 - 10)
TZD	0.35	7 (3 - 10)
BB+other	0.31	8 (2 - 10)
Other	0.26	9 (2 - 10)
BB+TZD	0.17	9 (2 - 10)

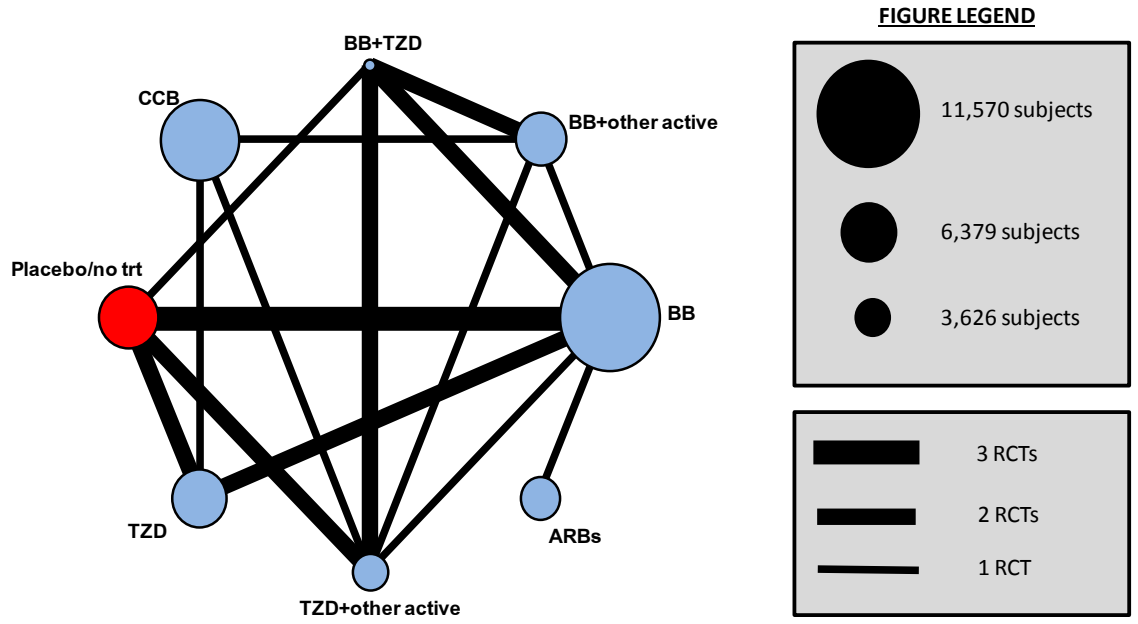
Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest incident cases of sexual dysfunction, second fewest incident cases of sexual dysfunction, and so forth is provided in **Table 11**. The control treatment was associated with the most favorable SUCRA value and median treatment rank.

4.3.2.8 Findings, Depression

Figure 16 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs. A total of 8 interventions were associated with RCTs that reported data on occurrences of depression across 15 RCTs,[27-30,32,34,40,41,53-55,57,75,111,112] with the numbers of trials and randomized patients per treatment ranging from 1 - 8 and 529 – 11,570 (median 5,970), respectively. Comparisons between BB with the reference treatment were most prevalent. Many comparisons of treatments were informed by single trials, and a number of comparisons have not been evaluated in head-to-head RCTs.

Figure 16:
Network Diagram, Depression (15 studies, 47,746 subjects, 3,126 events)



Joining lines indicate where head-to-head RCTs between interventions were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention.

Figure 17a provides a summary of the odds ratios against the control treatment, while **Figure 17b** presents a league table which summarizes all possible pairwise comparisons between included regimens.

Figure 17a: Forest Plot of Comparisons versus the Control Treatment, Depression – Summary Odds Ratios and Credible Intervals

Treatment	OR (95% CrI)	n/N
BB	1.08 (0.68 - 2.08)	1,032 / 11,571
TZDs	0.96 (0.48 - 1.73)	278 / 6,379
ARBs	1.02 (0.35 - 3.75)	358 / 4,605
CCB	1.23 (0.39 - 4.14)	328 / 8,771
BB+TZD	1.35 (0.48 - 3.83)	18 / 529
TZD+other active	1.72 (0.63 - 4.78)	192 / 3,626
BB+other active	1.02 (0.24 - 3.73)	186 / 5,562

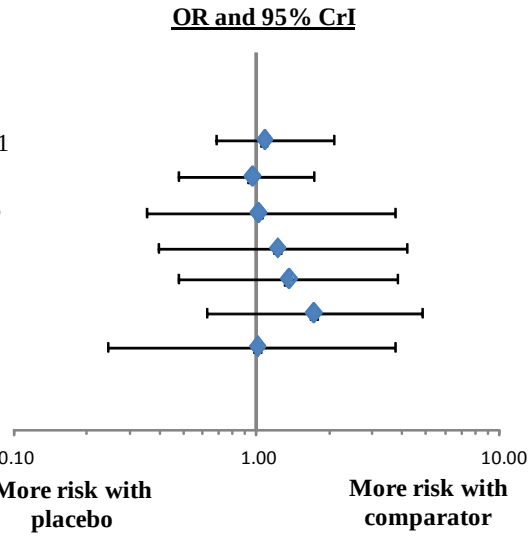


Figure 17b: League Table of all Pairwise Comparisons, Depression – Summary Odds Ratios and Credible Intervals

PL/ NO TRT	BB	TZD	ARB	CCB	BB+TZD	TZD+other	BB+other
1.08 (0.68 - 2.08)							
0.96 (0.48 - 1.73)	0.89 (0.38 - 1.54)						
1.02 (0.35 - 3.75)	0.97 (0.34 - 2.70)	1.07 (0.37 - 4.48)					
1.23 (0.39 - 4.14)	1.13 (0.32 - 3.75)	1.3 (0.41 - 4.68)	1.18 (0.23 - 5.57)				
1.35 (0.48 - 3.83)	1.24 (0.37 - 3.66)	1.42 (0.44 - 4.91)	1.3 (0.26 - 5.54)	1.1 (0.26 - 4.43)			
1.72 (0.63 - 4.78)	1.57 (0.50 - 4.49)	1.81 (0.61 - 5.78)	1.65 (0.34 - 6.76)	1.41 (0.54 - 3.22)	1.27 (0.35 - 4.65)		
1.02 (0.24 - 3.73)	0.94 (0.2 - 3.37)	1.07 (0.26 - 4.26)	0.98 (0.15 - 4.81)	0.84 (0.28 - 1.89)	0.76 (0.15 - 3.33)	0.59 (0.17 - 1.82)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of depression with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow.

- ***Comparisons against the control treatment (Figure 17a)***. None of the comparisons against the control treatment showed evidence of an increased risk of depression. All comparisons were associated with wide 95% credible intervals, and none approached statistical significance in the analysis.

- ***Comparisons between active agents (Figure 17b)***. Analogous to comparisons against the control treatment, comparisons between the different active interventions also did not

identify any statistically significantly increased risks of depression. Credible intervals were again very wide.

Table 12:
Summary of SUCRA and median ranks, depression

Treatment	SUCRA (%)	Median rank (95% CrI)
TZD	0.66	3 (1 - 7)
PL/no trt	0.62	4 (1 - 7)
BB+other	0.60	4 (1 - 8)
ARB	0.57	4 (1 - 8)
BB	0.53	4 (1 - 8)
CCB	0.45	5 (1 - 8)
BB+TZD	0.38	6 (1 - 8)
TZD+other	0.20	7 (2 - 8)

Treatments are ordered from highest to lowest SUCRA value (higher values are better).Median ranks with credible intervals are shown; ranks nearer 1 are better, while wider credible intervals show increased uncertainty.

- ***Treatment rankings***. A summary of estimates of the probabilities each regimen is associated with the fewest cases of depression, second fewest cases of depression, and so forth is provided in **Table 12**. The uncertainty surrounding pairwise comparisons was reflected in these parameters, including credible intervals around median rankings which were very wide. These parameters reinforce interpretations from the pairwise comparisons that there exists no clearly increased or reduced risk associated with a particular treatment based on the available trial data.

4.4 Overview, Other Network Meta-Analyses for Hypertension

During performance of our systematic review, additional NMAs evaluating anti-hypertensive therapies were published and. Here we provide an overview of findings from these publications for additional background information of relevance to this review. To identify these studies, a searched of PubMed was performed (November 7, 2013) using the terms *hypertension* and *network meta-analysis*, limiting eligible citations to meta-analyses as a study type. All reports considered similar intervention classes: placebo/control/standard care, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, alpha-blockers, and angiotensin receptor blockers were examined; few reviews considered combination therapy. Two reports examined comparative treatment effects for single drugs (e.g. 1 within the therapeutic class of diuretics and 1 within the beta-blockers class). The studies varied widely in terms of populations, outcomes, and findings.

- In 2003, Psaty et al[242] examined cardiovascular and cerebrovascular outcomes (congestive heart failure, coronary heart disease, stroke, cardiovascular disease events, cardiovascular disease mortality, and total mortality) in a series of NMAs of data from 42 RCTs of 7 major treatment strategies (diuretics, BB, CCBs, ACE inhibitors, ARBs, alpha-blockers and placebo) and 192,478 hypertensive patients. The review concluded that low dose diuretics were the best first-line agent for the prevention of cardiovascular and cerebrovascular disease morbidity and mortality.
- In 2007, Elliot and Meyer[243] reported findings from an NMA of 22 RCTs and 143,153 patients that compared the proportion of patients who developed diabetes during treatment. The occurrence of diabetes was found to be lowest with ARBs and ACE inhibitors, followed by CCBs and placebo, then BB and diuretics in rank order.
- In 2008, Coleman et al (2008)[244] studied the association between commonly used antihypertensive agents and the incidence of cancer in an NMA of 27 RCTs and 126,137 patients. The following antihypertensive drug classes were examined: TZD, BB, ACE-I, ARB or CCB. The authors concluded that commonly used antihypertensive drugs were not associated with increased odds of developing cancers.
- Against a background of an analysis showing increased risk of cancer with ARBs, Bangalore et al. (2011)[245] examined the risks of cancer incidence associated with the use of anti-hypertensive drugs in 324,168 participants in 70 trials, with no restrictions on morbidities. Amongst the broad range of participants, cancers were not increased among those taking antihypertensive medications such as ARB, ACE-I, BB, diuretics, and CCB, although increased risk with the combination of ACE-I and ARBs could not be ruled out.
- Fretheim et al (2012)[246] examined the comparative effectiveness of different classes of antihypertensive medication for primary prevention of cardiovascular disease in a NMA of 25 RCTs in healthy people at risk of cardiovascular disease. The authors concluded that there seems to be little to no difference between commonly used antihypertensives for primary prevention of cardiovascular disease.

There were two NMAs that looked at the relative effects of individual treatments for a therapeutic class. The NMA by Chatterjee et al (2013)[247] examined whether a particular beta-blocker is superior in patients with heart failure and reduced ejection fraction or whether the benefits of these agents are mainly due to a class effect. Twenty-one RCTs with 23,122 patients were included, focusing on atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, nebivolol,

placebo and/or standard of care. The primary endpoint was all-cause mortality. The authors concluded that the benefits of BB in patients with heart failure with reduced ejection fraction seem to be mainly due to a class effect, as no statistical evidence from current trials supports the superiority of any single agent over the others.

In a work by Roush et al (2012)[248], the authors evaluated the comparative effectiveness of the thiazide diuretics hydrochlorothiazide and chlorthalidone in reducing cardiovascular events. Nine RCTs were included. The authors concluded that chlorthalidone was superior to hydrochlorothiazide in preventing cardiovascular events. However, it was recognized that this effect cannot be attributed entirely to the lesser effect of hydrochlorothiazide on office systolic blood pressure, but rather may be attributed to the effects of alternative medications or to the short duration of action of hydrochlorothiazide.

Other network meta-analyses were also found, but were not relevant to the objectives of this review. [249-252] Overall, network meta-analyses of anti-hypertensive medications to date have largely focused on comparisons of monotherapies for treatment of hypertension. Examinations of benefits and harms of anti-hypertensive medications with respect to cardiovascular, incident diabetes and cancer risks have to date yielded different risk and benefit profiles across the range of common treatments. Knowledge regarding treatment of hypertension has evolved over the years, such that placebo-controlled trials are increasingly considered unethical. Thus, the inclusion of earlier trials in network meta-analyses is helpful to allow for indirect information for comparisons between active treatments. An additional challenge remains in that diet and lifestyle choices have also changed over time, potentially introducing heterogeneity in populations over time.

In summary, network meta-analyses have previously been performed to study the relative effects of anti-hypertensive medications; however, knowledge gaps, the age of some of the literature, disparities among the populations focused upon, and the lack of examination of a range of beneficial and adverse outcomes in a single, comprehensive dataset, indicated the need for the present study.

5. Discussion, Systematic Review Findings

5.1 Summary and Interpretations

In this systematic review, we explored the effects of different classes of antihypertensive therapies on a series of clinically important outcomes in non-diabetic patients with hypertension using network meta-analysis of randomized controlled trials. Trials randomizing patients to both single agents and combination therapies were considered in our treatment network to address the research questions of interest. Impact of the interventions studied on mortality (both overall and cardiovascular), myocardial infarction and stroke showed that all monotherapy and combination therapy regimens demonstrated some evidence of benefits relative to no treatment, however achievement of statistically significant differences varied by intervention and outcome. Some interventions demonstrated statistically significant benefits in terms of reducing risks versus placebo/no treatment for overall mortality (TZD+other active treatments, TZD, ARB, CCB; range of ORs 0.73-0.91), cardiovascular mortality (TZD+other active treatments, TZD, CCB;

range of ORs 0.65-0.87) and stroke (TZD+other active treatments, TZD, CCB, ARB; range of ORs 0.41-0.72). Only ACE-I (OR 0.66, 95% CrI 0.48-0.90) and TZD (OR 0.76, 95% CrI 0.57-0.99) demonstrated statistically significant benefits versus placebo/no treatment for MI. Many of the pairwise comparisons between active regimens did not identify statistically significant differences between interventions, though in several analyses there were limited numbers of studies for some regimens. We next provide discussion of findings with regard to the clinical research questions of interest in terms of monotherapies and combination therapies, followed by additional consideration of our results.

5.2 Summary of Findings Regarding A Priori Research Questions

The first research question in this review sought to evaluate the effects of TZD monotherapy in comparison to the effects of other monotherapy interventions. With regard to impact on mortality, stroke and MI, pairwise comparisons of TZD versus control were associated with statistically significant benefits. However, pairwise comparisons with active monotherapy interventions (ACE-I, ARB, BB and CCB) generally did not rule out potential null differences between treatments. Regarding harms, TZD were found to be associated with highly increased risks of both incident diabetes compared to no treatment; this increased risk remained statistically significant for incident diabetes when TZD were compared against ACE-I, ARB and CCB. Secondary measures (i.e. SUCRA and treatment rankings) identified TZD as preferable for MI and stroke reduction while reinforcing concerns about incident diabetes occurrence.

The second research question sought to assess the benefits of TZD-based combination therapies relative to other combination therapies. We classified combination regimens in our treatment networks according to the groups of TZD+other active agents, TZD+BB, abd BB+other active agents. Due in part to our eligibility criteria, we identifed a relatively small number of studies involving combination therapy; we also did not have available evidence in our treatment networks on some combination regimens relevant to clinical practice including regimens such as ACE-I+CCB, TZD+CCB, and so forth. Analyses for mortality outcomes, stroke and MI all demonstrated strong and statistically significant benefits of TZD+other active agents compared to most other monotherapies and combination therapies. The size of these effects exceeded the expectations of participating clinical experts; given challenges in the evidence base and geometry structure of our treatment network (i.e. minimal head-to-head studies on this regimen, sample size, indirectness of evidence, and so forth), the size of these benefits should be interpreted very cautiously in terms of decision-making. Past clinical guidance has suggested that combination therapy with BB+TZD is effective, however the relatively small amount of data presented challenges in this work. BB+TZD has demonstrated clinical benefits previously, however some clinical guidelines[253] note this regimen may be associated with concerns regarding incident diabetes, and other combinations (e.g. TZD+ACE-I, TZD+ARB, ACE-I+CCB) are also effective. As with TZD monotherapy, combination therapy involving TZD with other active agents showed an increased risk of incident diabetes in our work relative to CCB, ARB and ACE-I.

5.3 Additional Considerations and Discussion

In Section 4.4 we provided some description of findings previously reported in existing network meta-analyses studying pharmacotherapies for hypertension. The findings generated from the included selection of RCTs meeting our eligibility criteria pertaining to patients without diabetes

in many cases compared generally well with existing works. However, it was unexpected that the evidence related to the study of TZD, ACE-I and ARB did not demonstrate stronger, statistically significant benefits for overall or cardiovascular mortality compared to no treatment. That ARB did not show a benefit similar to ACE-I for myocardial infarction was also unexpected, and may be due to certain studies not entirely meeting our inclusion criteria. Benefits of different therapies have been associated with varied trends in other recent systematic reviews, suggesting some lack of clarity about the magnitude of benefits of some therapies. For example, van Vark et al noted a 10% risk reduction for all-cause mortality associated with ACE-I but not ARBs compared to control[254] Bangalore et al also did not identify a benefit of ARBs in comparison to control with regard to mortality [255] A 2014 meta-analysis in diabetic patients noted a mortality benefit for ACE-I but not for ARB.[256] Regarding analyses that reflected clinical subgroups of lesser cardiovascular risk and moderate/high cardiovascular risk, it was common in the former group, due to a paucity of trial data, for interventions to fall out of our treatment network and for uncertainty to be high. In the latter higher risk group, given that this population was enrolled in the greater majority of included trials, findings from all encompassing analyses were generally comparable.

In terms of harms, our network meta-analyses identified increased risks of incident diabetes associated with TZD monotherapy as well as combination therapy involving TZD with other active agents when compared to no treatment; this was in line with our expectations and with findings from a 2007 network meta-analysis by Elliot and Meyer[243], and magnitudes of effect are similar between our work and theirs. These regimens also demonstrated increased risks compared to CCB, ARB and ACE-I.[257,258] Our analyses did not suggest the presence of clear benefits for any particular intervention for this outcome, however power was limited given the rarity of the outcome and the small number of studies. Network meta-analyses for incident cancers and depression were associated with wide 95% credible intervals for all comparisons between treatments in the treatment network, and did not identify any differential risks between therapies. Coleman et al[244] also failed to find any important differences between classes in terms of cancer risk in a 2008 network meta-analysis. In 2010, a meta-analysis of RCTs by Sipahi at al[259] suggested that ARBs were associated with a modestly increased risk of new cancers. Since then, additional reviews investigating cancer risk for anti-hypertensives including ARBs have become available.[260,261]). Although these analyses included most of the available randomized evidence, an association was not established. Bangalore et al[245], however, concluded that an increased risk of cancer with the combination of ACE inhibitors and ARBs cannot be ruled out – this was largely influenced by the findings in the ONTARGET trial.[262] The combination of ACE inhibitors and ARBs was not evaluated in any of the trials that met the inclusion criteria for our review. Regarding depression, while the perception amongst clinicians has long been that BB are associated with an increased incidence, our data and analyses could not confirm this perception. Monotherapy and combination therapies involving TZDs were associated with a greater risk of sexual dysfunction compared to the reference group and might also be compared to other active treatments, however credible intervals for the latter comparison were extremely wide and thus no definitive statements are possible based on our data.

5.4 Limitations of the Systematic Review

There are limitations in our review which are important to note. While we have made efforts where feasible to address these challenges in our methods, they should be kept in mind from the perspective of interpretations.

- Our review excluded a number of large trials in the field of hypertension. While inclusion of these trials could change our findings both in terms of reducing statistical uncertainty and possibly changing the magnitude of treatment effects, these studies did not meet our eligibility criteria regarding either (i) the proportion of non-diabetic participants in the study, or (ii) providing subgroup data for non-diabetic patients. Some of these studies could have been included in our review if a less stringent criteria for proportion of diabetic patients was selected.
- We did not perform a comprehensive literature search for all primary RCTs meeting our selection criteria. However, we used established methods to leverage a large number of existing systematic reviews to identify relevant studies and we believe this technique has performed well.
- As noted in the methods section of the report, an important limitation of many trials included in this review is the existence of background/prior antihypertensive medications and the inclusion of step-up therapy during trials. We adopted a classification strategy for treatments in this review consistent with past network meta-analyses and systematic reviews in hypertension by classifying trial arms according to the first regimen patients received following randomization. However, in general such a strategy may result in misunderstanding of agents' relative benefits and be a function of variation in blood pressure targets across trials. While we have used the terminology *monotherapy* and *combination therapy* in this report based on randomized treatments, the common prior history/use of additional medications means that data should be interpreted carefully. Pre-existing therapies are not always clearly reported in trials of hypertension medications and presents a challenge to treatment classification.
- We followed prior network meta-analyses in the approach of formulating our comparisons at the drug class level. Readers are however cautioned to consider that not all agents from each pharmacologic class are represented in the RCTs that formed our evidence base for network meta-analyses. Our range of agents reflected within each class may also be more narrow than other network meta-analyses in this field because our research questions required additional restriction criteria related to diabetes which was associated with the exclusion of assorted trials.
- Reporting of study characteristics including duration of follow-up, participant ethnicity, presence of industry funding and other such traits was inconsistent across included trials. Variations over time in patient populations, the use of co-interventions, and other such features were also present. To the extent possible, we pursued sensitivity analyses to establish the robustness of our findings, which appears to be strong.
- There was considerable variation in the availability of data across outcomes in this review. While a total of 88 trials met our eligibility criteria, the largest number included in any single analysis was 62 (overall mortality); the number of available studies ranged between 30-40 for our other three efficacy outcomes, and dropped as low as a minimum of 15 studies for our harms of interest. While this rise and fall of numbers may be partially related to the primary goals of particular studies, it also suggests the potential existence of selective outcome reporting from study to study.
- We identified minimal study data meeting our inclusion criteria for alpha blocker treatments. A recent review highlights that the majority of study information for this class has evaluated changes in blood pressure and not the hard outcomes that were of interest in our systematic review.[263] As a consequence, we could not evaluate its benefits in our networks.

- In addition to the outcome measures analyzed and presented in this report, we collected information from eligible studies for other outcomes including adherence and time in therapeutic blood pressure range. Due to few trials reporting the latter measure as well as definitions from study to study being highly heterogeneous, these outcomes were not judged amenable for our meta-analyses and were considered of minimal interest by our experts. We would be happy to discuss this data further with our requestors if there is additional interest in this information. While not included in our original study protocol as an outcome of interest because it is commonly considered only a proxy measure for benefits, our clinical experts indicate it may be worthwhile to also compare on-treatment blood pressure changes in the included trials to establish whether this is the primary explanation for findings observed in our analyses.

5.5 Conclusions from this Systematic Review

Based on findings from network meta-analyses of randomized controlled trials, we performed class level analyses of pharmacotherapies across a range of both effectiveness and harms outcomes in a population of patients without diabetes. While all agents showed at least some evidence of benefit, not all agents consistently showed statistically significant improvements across our effectiveness measures of overall mortality, cardiovascular mortality, stroke and myocardial infarction. Regarding the benefits of TZD monotherapy relative to other monotherapy interventions, comparisons for mortality measures, stroke and MI generally identified no differences, however an increased risk of incident diabetes was noted. Regarding combination therapy involving TZD (as assessed here with BB and with other active agents), TZD with other active agents was associated with the largest treatment effect compared to no treatment for overall mortality, cardiovascular mortality and stroke, and demonstrated statistically significant benefits over other classes in many comparisons. Because of challenges in our evidence base and network structure (in terms of sometimes few head-to-head studies, sample size and indirectness of evidence) the size of tese benefits should be interpreted cautiously for decision-making purposes. From a harms perspective, TZD increased the risks of incident diabetes in our analyses. We did not find information suggesting any increased risk of cancers or depression based on the data from our included trials. The challenges of confounding based on use of background medications should also be considered.

6. Primary Economic Evaluation

The objective of the economic component of this study was to determine the cost effectiveness of alternative pharmacological treatments for hypertension. The study did not consider the cost effectiveness of alternate strategies relating to sequencing of therapies. Thus, the study focused on the impact of long-term costs and outcomes (life years and QALYs) using seven alternate drug interventions: thiazide diuretics (TZD), calcium channel blockers (CCB), beta blockers (BB), ACE inhibitors (ACE-I), angiotensin receptor blockers (ARB), and the combination regimens of BB+TZD and TZD+ARB.

6.1 Methods for Economic Evaluation

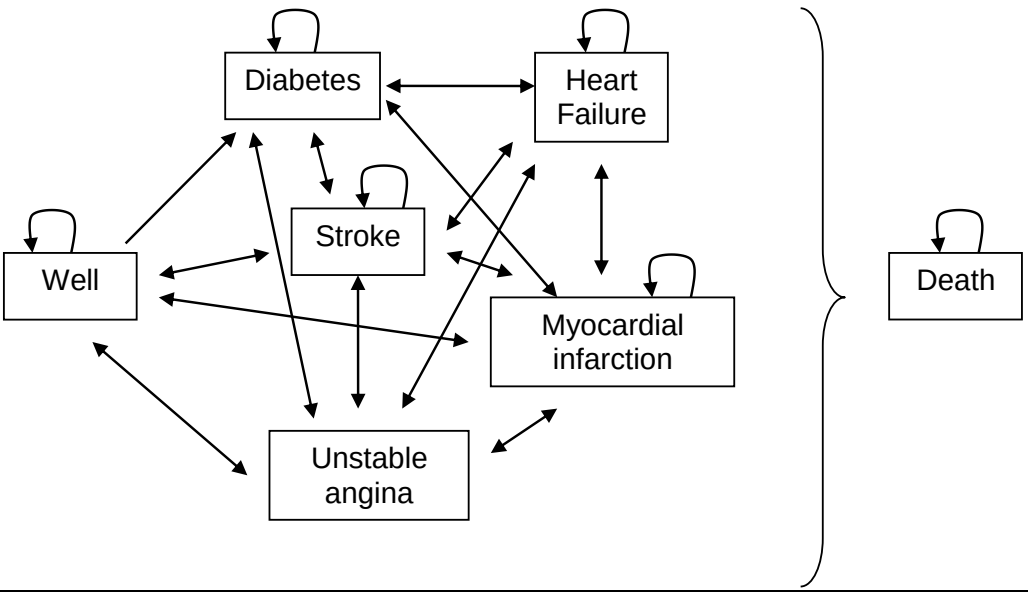
6.1.1 Study Population

For the base case analysis, eight study populations were considered. The cohorts included men and women, 55 or 65 years of age, with a baseline risk of diabetes of 1.1%, heart failure of 1% and CVD of between 2% and 3.2% (dependent on age and gender). The base case scenario assumed no prior history of diabetes or cardiovascular/cerebrovascular event.

6.1.2 Model structure

A Markov Model developed within a Microsoft Excel spreadsheet similar to the model used within a prior review conducted for the Canadian Agency for Drugs and Technologies in Health (CADTH) was used.[264] **Figure 18** contains a simplified representation of the model. The model adopts a time horizon of twenty years with a cycle length of six months. After ten years, the clinical effects and costs of anti-hypertensive treatment were excluded due to concerns over waning of treatment effect.

Figure 18: Schematic representation of Markov model



Arrows indicate possible between-state transitions patients may experience during each model cycle. Auto-loops indicate states where patients can potentially remain in the same state for more than one model cycle.

The model was populated with estimates of transition probabilities, treatment effects, costs and utilities. Published studies including previous economic models were searched to identify the most recent reliable estimates for all parameters within the model based on their relevance to the study question, study population and study perspective.

In the model, all patients are assumed to start in a "well" state which represents no previous additional CV or CRV events. Patients can transition from the well state to states representing the progression of CV and CRV diseases and the incidence of diabetes. Transition probabilities from the well-state are a function of gender, age and diabetes and cerebrovascular/ cardiovascular risk. States relate to unstable angina, MI, CV disease, stroke, HF and/or diabetes. Once a patient experiences one of these events, the annual risks of further events become a function of their previous disease history.

6.1.3 Transition probabilities

For each study population assuming no drug therapy, transition probabilities relating to the transition from the "well" state were calculated as follows. As per the previous CADTH technology assessment, these were derived from a Canadian nomogram used in clinical practice to predict cardiovascular and cerbrovascular risks.[265] In addition, the probability of non-cardiovascular death was obtained from Statistics Canada data.[266]

Once the individual had experienced an initial event, the risk of them experiencing a subsequent event would be affected by their disease history. The probabilities of further events were derived from the same sources as the aforementioned CADTH analysis.[267,268]

To incorporate the effect of treatment on the transition of patients, the transition probabilities identified above were weighted by the relative risks of MI, stroke, diabetes and cardiovascular mortality associated with treatment obtained from the network meta analyses presented in this report. The same risk reductions are used for all patient cohorts.

6.1.4 Costs

The direct cost of drug therapy and the costs associated with long-term complications of hypertension were incorporated into the model. All costs included in the model were Canadian 2014 costs. In the base case scenario, the annual cost of drug therapy was calculated based on the most commonly used drug and dosage within each class of medications. Annual drug costs were obtained from the Ontario Drug Benefit Formulary Comparative Drug Index weighted by an 8% pharmacy mark-up and included four dispensing fees of $8.83 assuming the maximum 90 day supply.[269]

Canadian specific costs associated with the complications of hypertension were obtained a recent Canadian study.[270] Costs related to both the incident event (cost in the first six months) and to the incremental costs of subsequent long-term management (costs in subsequent six month cycles). For patients with more than one previous complication, an additive model was assumed with respect to costs.

6.1.5 Utilities

For patients in the well-state, the Canadian population age-gender specific norms from the Canadian Community Health Survey (CCHS) exclusive of patients with CHD. Stroke and/or

diabetes were used.[271] For the other disease states within the model, utility weights were derived from the literature as per the previous CADTH report.[264] For patients with disease complications, the impact of further disutilities was modeled using a multiplicative assumption.

6.1.6 Analysis

Analysis is presented in terms of the incremental cost per quality adjusted life year (QALY) gained. A sequential analysis is conducted such that, all treatments which are dominated (higher cost, less QALYs) by at least one other treatment are excluded. Then, incremental cost effectiveness ratios (ICERs) are discussed for remaining treatment options. Analysis is conducted from the perspective of a provincial ministry of health. Costs and benefits were discounted at 5% per annum.[272] The base analysis is for a Male aged 65. Further analyses are presented varying age and gender.

6.2 Results from Economic Evaluation

For a male aged 65, no therapy, BB, TZD, ARB and CCB are subject to dominance or extended dominance. Of the non-dominant options, ACE-I is the least costly option. The incremental cost per QALY gained for BB+TZD versus ACE-I is $20,917. For TZD+ARB versus BB+TZD the incremental cost per QALY gained is $135,281.

Table 13: Cost Effectiveness Results for Males aged 65				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$18,595	7.50	9.36	
BB+TZD	$19,417	7.54	9.43	$20,917.07
TZD+ARB	$21,681	7.55	9.49	$135,280.76
No therapy	$18,902	7.37	9.22	Dominated by ACE-I
BB	$19,515	7.38	9.25	Dominated by ACE-I
TZD	$19,235	7.45	9.33	Dominated by ACE-I
ARB	$19,931	7.52	9.39	Extended dominace through ACE-I and BB+TZD
CCB	$19,481	7.52	9.41	Extended dominace through ACE-I and BB+TZD

Results were fairly consistent across patient populations, although for females aged 75 and over, the incremental cost per QALY gained for TZD+ARB versus BB+TZD was less than $50,000.

Table 14: Cost effectiveness Results for Males aged 45				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$23,308	9.05	10.99	
BB+TZD	$24,345	9.07	11.04	$51,713.76
No therapy	$23,982	8.91	10.84	Dominated by ACE-I
BB	$24,658	8.91	10.85	Dominated by ACE-I
TZD	$24,256	8.96	10.92	Dominated by ACE-I
ARB	$25,266	9.07	11.03	Extended dominace through ACE-I, BB+TZD
TZD+ARB	$27,067	9.05	11.05	Extended dominace through ACE-I, BB+TZD
CCB	$24,630	9.06	11.02	Extended dominace through ACE-I, BB+TZD

Table 15: Cost effectiveness Results for Males aged 55				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$21,331	8.44	10.37	
BB+TZD	$22,199	8.48	10.44	$21,681.27
No therapy	$21,634	8.28	10.21	Dominated by ACE-I
BB	$22,268	8.30	10.24	Dominated by ACE-I
TZD	$21,991	8.38	10.34	Dominated by ACE-I
ARB	$22,641	8.47	10.42	Extended dominace through ACE-I, BB+TZD
TZD+ARB	$24,662	8.47	10.48	Extended dominace through ACE-I, BB+TZD
CCB	$22,205	8.47	10.43	Extended dominace through ACE-I, BB+TZD

Table 16: Cost effectiveness Results for Males aged 75				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$15,161	5.91	7.89	
BB+TZD	$15,850	5.95	7.95	$19,042.12
TZD+ARB	$17,735	5.97	8.02	$65,986.91
No therapy	$15,368	5.81	7.77	Dominated by ACE-I
BB	$15,905	5.82	7.79	Dominated by ACE-I
TZD	$15,665	5.88	7.87	Dominated by ACE-I
ARB	$16,291	5.92	7.91	Extended dominace through ACE-I, BB+TZD
CCB	$15,899	5.93	7.93	Extended dominace through ACE-I, BB+TZD

Table 17: Cost effectiveness Results for Males aged 85				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$9,638	3.62	5.37	
BB+TZD	$10,095	3.64	5.41	$20,601.19
TZD+ARB	$11,395	3.66	5.46	$63,926.81
No therapy	$9,852	3.56	5.30	Dominated by ACE-I
BB	$10,206	3.57	5.31	Dominated by ACE-I
TZD	$9,930	3.60	5.36	Dominated by ACE-I
ARB	$10,527	3.62	5.38	Extended dominace through ACE-I, BB+TZD
CCB	$10,171	3.62	5.39	Extended dominace through ACE-I, BB+TZD

Table 18: Cost effectiveness Results for Females aged 45				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$21,758	8.79	10.84	
BB+TZD	$22,551	8.83	10.91	$18,396.92
No therapy	$21,620	8.63	10.66	Dominated by ACE-I
BB	$22,353	8.65	10.70	Dominated by ACE-I
TZD	$22,327	8.72	10.80	Dominated by ACE-I
ARB	$22,560	8.83	10.89	Extended dominace through ACE-I, BB+TZD
TZD+ARB	$24,769	8.82	10.95	Extended dominace through ACE-I, BB+TZD
CCB	$22,346	8.82	10.90	Extended dominace through ACE-I, BB+TZD

Table 19: Cost effectiveness Results for Females aged 55				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$20,153	8.49	10.51	
BB+TZD	$20,942	8.54	10.58	$17,173.77
No therapy	$20,069	8.34	10.34	Dominated by ACE-I
BB	$20,790	8.36	10.37	Dominated by ACE-I
TZD	$20,743	8.43	10.48	Dominated by ACE-I
ARB	$21,006	8.53	10.56	Extended dominace through ACE-I, BB+TZD
TZD+ARB	$23,136	8.55	10.64	Extended dominace through ACE-I, BB+TZD
CCB	$20,773	8.52	10.57	Extended dominace through ACE-I, BB+TZD

Table 20: Cost effectiveness Results for Female aged 65				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$17,467	7.78	9.85	
BB+TZD	$18,272	7.82	9.91	$20,661.81
TZD+ARB	$20,266	7.85	9.99	$59,888.05
No therapy	$17,418	7.66	9.70	Dominated by ACE-I
BB	$18,187	7.66	9.72	Dominated by ACE-I
TZD	$18,169	7.72	9.80	Dominated by ACE-I
ARB	$18,545	7.79	9.87	Extended dominace through ACE-I, BB+TZD
CCB	$18,261	7.79	9.88	Extended dominace through ACE-I, BB+TZD

Table 21: Cost effectiveness Results for Female aged 75				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$14,657	6.43	8.69	
BB+TZD	$15,351	6.47	8.75	$18,317.57
TZD+ARB	$17,053	6.51	8.84	$40,846.14
No therapy	$14,526	6.33	8.56	Dominated by ACE-I
BB	$15,231	6.34	8.57	Dominated by ACE-I
TZD	$15,238	6.39	8.65	Dominated by ACE-I
ARB	$15,551	6.44	8.70	Extended dominace through ACE-I, BB+TZD
CCB	$15,316	6.45	8.72	Extended dominace through ACE-I, BB+TZD

Table 22: Cost effectiveness Results for Female aged 85				
Intervention	**Costs**	**QALYs**	**Life years**	**Sequential ICER**
ACE-I	$9,270	4.15	6.08	
BB+TZD	$9,718	4.18	6.13	$18,288.40
TZD+ARB	$10,836	4.21	6.19	$37,302.19
No therapy	$9,139	4.09	6.00	Dominated by ACE-I
BB	$9,646	4.10	6.01	Dominated by ACE-I
TZD	$9,594	4.13	6.06	Dominated by ACE-I
ARB	$9,906	4.16	6.09	Extended dominace through ACE-I, BB+TZD
CCB	$9,697	4.16	6.10	Extended dominace through ACE-I, BB+TZD

6.3 Summary of Findings, Economic Evaluation

Regarding the third research question of interest, this economic analysis found little to choose from between each of the drug treatments in terms of effectiveness, with results primarily driven by drug costs. In terms of cost effectiveness, the results suggest that treatment with BB in combination with TZD is the most cost effective treatment option for men and women aged less than 75 and for women aged 75 and over ARB in combination with TZD is the most cost effective option. In terms of limitations, this economic evaluation can be seen solely as an initial exploration of the cost effectiveness of alternate drug classes in the treatment of hypertension. Given the limited resources available for this analysis in conjunction with our sizable clinical review, a more comprehensive analysis of uncertainty (both deterministic and probabilistic) was not feasible. Analysis is restricted to a patient population without previous event history. A fuller analysis of variability would explore the impact of prevalent disease on the cost effectiveness of treatments.A more comprehensive analysis would also explore any differential results in terms of cost effectiveness within drug classes.

APPENDICES

- **Appendix 1:** Literature Search Strategy
- **Appendix 2:** Summary Tables of Study Characteristics
- **Appendix 3:** Summary of Traditional Pairwise Meta-Analyses
- **Appendix 4:** Summary of Model Fit Statistics from Primary Network Meta-Analyses
- **Appendix 5:** Summary of Findings from Network Meta-Regression Analyses and Subgroup Analyses
- **Appendix 6:** Data Elements for Economic Evaluation

Appendix 1: Medline Literature Search Strategy

1. exp Hypertension/
2. hypertens*.tw.
3. ((high* or rais* or elevat* or heighten* or increas*) adj3 ("blood pressure" or "diastolic pressure" or "systolic pressure" or "pulse pressure")).tw.
4. ((high* or rais* or elevat* or heighten* or increas*) adj3 (BP or DBP or SBP)).tw.
5. exp Cardiovascular Diseases/pc [Prevention & Control]
6. ((borderline or pre-disease* or pre-clinical* or preclinical* or sub-clinical* or subclinical* or pre-morbid* or premorbid* or risk* or susceptib* or pre-dispos* or predispos* or predict* or probabilit* or likelihood or likeliness or prevent*) adj3 (cardiovascular or cardiometabolic* or cardio-metabolic* or coronary disease* or heart disease* or heart attack* or heart failure or myocardial infarction* or coronary artery disease* or CVD or peripheral artery disease* or PAD or CHD or CAD or arteriosclerosis or atherosclerosis or stroke)).tw.
7. or/1-6
8. exp hypertension/dt [drug therapy]
9. exp Sodium Chloride Symporter Inhibitors/
10. ((thiazide or benzothiadiazine or benzo-thiadiazine or potassium depleting) adj1 diuretic$1).tw.
11. (sodium chloride symporter inhibitor$1 or sodium chloride cotransporter inhibitor$1 or sodium chloride co-transporter inhibitor$1 or thiazide sensitive NaCl cotransporter inhibitor$1 or thiazide sensitive NaCl co-transporter inhibitor$1).tw.
12. exp Chlorothiazide/
13. (chlorothiazide or Alurene or Chlorosal or Chlotride or Chlorothiazid or Chlorothiazidum or Chlorthiazid or Chlorthiazide or Chlorthiazidum or Chlortiazid or Chlorurit or Chlotride or Clorotiazide or Clotride or Diuresal or Diuril or Diurilix or Diurite or Diutrid or Flumen or Minzil or Neo-dema or SK-Chlorothiazide or Salisan or Salunil or Saluretil or Saluric or Thiazide or Urinex or Warduzide or Yadalan).tw.
14. 58-94-6.rn.
15. exp Chlorthalidone/
16. (chlorthalidone or Apo-Chlorthalidone or Chlorphthalidolone or Chlorphthalidone or Chlortalidone or Chlortalidonum or Chlorthalidon or Clortalidone or Famolin or Hydro-Long or Hygroton or Igroton or Isoren or Natriuran or Oksodolin or oxodolin or Oradil or Oxodolin or Phthalamodine or Phthalamudine or Racemic chlorthalidone or Renon or Saluretin or Thalitone or Urolin or Zambesil).tw.
17. 77-36-1.rn.
18. exp Hydrochlorothiazide/
19. (Hydrochlorothiazide or "Aquazide H" or Apo-Hydro or Carozide or Dichlothiazide or Dihydrochlorothiazide or Esidrex or Esidrix or Ezide or HCTZ or Hydrochlorot or HydroDIURIL or Hydro-par or HydroSaluric or Hypothiazide or Microzide or Oretic or Sectrazide).tw.
20. 58-93-5.rn.
21. exp Hydroflumethiazide/
22. (Hydroflumethiazide or Bristab or Bristurin or Di-ademil or Di-adenil or Dihydroflumethiazide or Diucardin or Diuredemina or Diurometon or Elodrin or Elodrine or Enjit or Finuret or Flutizide or Hydol Hydrenox or Hydroflumethiazide or Hydroflumethiazidum or Hydroflumethizide or Idroflumetiazide or Leodrine or NaClex or Olmagran or Rivosil or Robezon or Rodiuran or Rontyl or saluron or Sisuril or Spandiuril or Trifluoromethylhydrothiazide or Vergonil).tw.
23. 135-09-1.rn.
24. exp Indapamide/
25. (indapamide or Arifon or Bajaten or Cormil or Damide or Fludex or Indaflex or Indapamide or Indamol or Ipamix or Lozol or Metindamide or Natrilix or Noranat or Pressurai or Tandix or Tertensif or Veroxil).tw.
26. 26807-65-8.rn.
27. exp Methyclothiazide/
28. (methyclothiazide or Aquatensen or Enduron or Naturon).tw.
29. 135-07-9.rn.

30. exp Metolazone/
31. (metolazone or Diulo or Microx or Mykrox or Oldren or Zaroxolyn or Zytanix).tw.
32. 17560-51-9.rn.
33. exp Polythiazide/
34. (Polythiazide or Drenusil or Nephril or Polythiazidum or Renese).tw.
35. 346-18-9.rn.
36. exp Angiotensin-Converting Enzyme Inhibitors/
37. ((Angiotensin-Converting Enzyme or Angiotensin I-Converting Enzyme or ACE or Kininase II) adj (inhibitor* or antagonist*)).tw.
38. (ACEI or ACEIs).tw.
39. exp Captopril/
40. (Acediur or Aceplus or Acepress or Acepril or Alopresin or Asisten or Capoten or Captolane or Captopril or Captoprilum or Captopryl or Captoril or Cesplon or Dilabar or Farcopril or Garranil or Hypertil or Hypopress or Isopresol or "L-Captopril" or Lopirin or Lopril or Novocaptopril or Tenosbon or Tensoprel or Zapto).tw.
41. 62571-86-2.rn.
42. exp Enalapril/
43. (Enalapril or Bonuten or Enalaprila or Enalaprilum or Gadopril or Kinfil).tw.
44. 75847-73-3.rn.
45. exp Lisinopril/
46. (Lisinopril or Lisinopril dehydrate or Prinivil or Renacor or Zestril).tw.
47. 83915-83-7.rn.
48. (Benazepril hydrochloride or Benazepril HCl or Briem or Cibace or Cibacen or Cibacen CHF or Cibacene or Labopol or Lotensin or Lotrel or Tensanil or Zinadril).tw.
49. benazepril.rn.
50. exp Fosinopril/
51. (Fosinopril or Dynacil or Fosenopril or Fosinil or Fosinorm or Fositens or Fozitec or Hiperlex or Monopril or Newace or Staril or "Tenso Stop" or Tensocardil).tw.
52. 98048-97-6.rn.
53. exp Ramipril/
54. (Ramipril or Acovil or Altace or Carasel or Cardace or Delix or Hytren or Lostapres or Naprix or Pramace or Quark or Ramace or Ramiprilum or Ramipro or Triatec or Tritace or Vesdil or Zabien).tw.
55. 87333-19-5.rn.
56. (Quinapril hydrochloride or Accupril or Accuprin or Accupron or Acequin or Acuitel or Acuprel or Asig or Conan or Continucor or Ectren or Hemokvin or Korec or Koretic or Lidaltrin or Quinapril or Quinapril HCl or Quinazil).tw.
57. 82586-55-8.rn.
58. exp Perindopril/
59. (Aceon or Covapril or Coversyl or Perindopril or Pirindopril or Prestarium).tw.
60. 82834-16-0.rn.
61. (Trandolapril or Gopten or Mavik or Odrik or Udrik).tw.
62. 87679-37-6.rn.
63. (Moexiril or Fempress or Moex or Moexipril hydrochloride or Perdix or Univasc).tw.
64. 103775-10-6.rn.
65. exp Calcium Channel Blockers/
66. ((calcium or ca) adj2 (blocker* or blockader* or blocking or antagonist* or inhibitor*)).tw.
67. exp Amlodipine/
68. (Amlodipine or Amlodipine Besylate or Amlodipine Maleate or Amlodis or Amlor or Astudal or Coroval or Istin or Lipinox or Norvasc).tw.
69. 88150-42-9.rn.
70. (Aranidipine or Sapresta).tw.
71. 86780-90-7.rn.
72. (Azelnidipine or Calblock).tw.

73. 123524-52-7.rn.
74. (Barnidipine or Cyress or HypoCa or Libradin or Mepirodipine).tw.
75. 104713-75-9.rn.
76. (Benidipine or Benidipinum or Coniel).tw.
77. 105979-17-7.rn.
78. (Cilnidipine or Atelec or Cinalong or Siscard).tw.
79. 132203-70-4.rn.
80. (Clevidipine or Cleviprex).tw.
81. clevidipine.rn.
82. exp Isradipine/
83. (Isradipine or Dynacirc or "DynaCirc CR" or Isradipinum or Lomir or Prescal).tw.
84. 75695-93-1.rn.
85. (Efonidipine or Landel).tw.
86. efonidipine.rn.
87. exp Felodipine/
88. (Felodipine or Agon or Felo Biochemie or Felo-Puren or Felobeta or Felocor or Felodipin or Felodur or Felogamma or Fensel or Flodil or Modip or Munobal or Perfudal or Plendil or Renedil).tw.
89. 72509-76-3.rn.
90. (Lacidipine or Lacidipinum or Lacimen or Lacipil or Motens).tw.
91. 103890-78-4.rn.
92. (Lercanidipine or Lacidipinum or Lercadip or Lerdip or Zanidip).tw.
93. 103890-78-4.rn.
94. (Manidipine or Calslot or Madipine or Franidipine).tw.
95. 89226-50-6.rn.
96. exp Nicardipine/
97. (Nicardipine or Antagonil or Carden SR or Cardene or Dagan or Flusemide or Lecibral or Lincil or Loxen or Lucenfal or Nicardipinum or Perdipine or Ridene or Vasonase).tw.
98. 55985-32-5.rn.
99. exp Nifedipine/
100. (Nifedipine or Adalat or Afeditab or Citilat or Cordipin or Cordipine or Corinfar or Fenihidin or Fenihidine or Fenigidin or Korinfar or Nifediac or Nifedical or Nifangin or Oxcord or Procardia or Procardia XL or Vascard).tw.
101. 21829-25-4.rn.
102. (Nilvadipine or Escor or Nivadil or Nilvadipinum).tw.
103. 75530-68-6.rn.
104. exp Nimodipine/
105. (Nimodipine or Admon or Brainal or Calnit or Kenesil or Modus or Nimodipin or Nimodipinum or Nimotop or Periplum or Remontal).tw.
106. 66085-59-4.rn.
107. exp Nisoldipine/
108. (Nisoldipine or Baymycard or Nisocor or Nisoldipinum or Sular or Syscor).tw.
109. 63675-72-9.rn.
110. exp Nitrendipine/
111. (Nitrendipine or Balminil or Bayotensin or Baylotensin or Baypresol or Baypress or Cardif or Gericin or Jutapress or Nidrel or Niprina or Nitre AbZ or Nitre-Puren or Nitregamma or Nitren 1A Pharma or Nitren acis or Nitren Lich or Nitrend KSK or Nitrendepat or Nitrendi Biochemie or Nitrendidoc or Nitrendimerck or Nitrepin or Nitrendipin or Nitrendipino or Nitrensal or Nitrepress or Nitrendipinum or Tensogradal or Trendinol or Vastensium).tw.
112. 39562-70-4.rn.
113. (Pranidipine or Acalas).tw.
114. 99522-79-9.rn.
115. exp Verapamil/

116. (Verapamil or Calan or Cordilox or Dexverapamil or Dilacoran or Falicard or Finoptin or Iproveratril or Isoptimo or Isoptin or Isoptine or Izoptin or Lekoptin or Vasolan or Verapamilum or dl-Verapamil).tw.
117. 52-53-9.rn.
118. exp Diltiazem/
119. (Diltiazem or Aldizem or Cardil or Cardizem or Cardizem LA or Dilacor or Dilacor XR or Dilcontin or Dilren or Dilta-Hexal or Diltiazem Hydrochloride or Diltiazem Malate or Diltiazemum or Dilticard or Dilzem or Endrydil or Incoril AP or Tiazac).tw.
120. 42399-41-7.rn.
121. exp Mibefradil/
122. (mibefradil or Posicor).tw.
123. 116644-53-2.rn.
124. exp Bepridil/
125. (Bepridil or Bedapin or Bepadin or Cordium or Unicordium or Vascor).tw.
126. 64706-54-3.rn.
127. exp Fluspirilene/
128. (fluspirilene or Fluspi or Fluspirilenum or Imap or Kivat or Redeptin).tw.
129. 1841-19-6.rn.
130. exp Aldosterone Antagonists/
131. (aldosterone adj (antagonist* or inhibit*)).tw.
132. exp Spironolactone/
133. (spironolactone or Acelat or Aldace or Aldactone or Alderon or Aldopur or Almatol or Altex or Aquareduct or Berlactone or duraspiron or Diatense or Espironolactona or Euteberol or Flumach or Frumikal or Jenaspiron or Novo-Spiroton or Practon or Spiractin or Spiresis or Spirobeta or Spirogamma or Spirolactone or Spirolang or Spirono-Isis or Spironone or Spirospare or Uractone or Urusonin or Veroshpiron or Verospiron or Verospirone or Xenalon).tw.
134. 52-01-7.rn.
135. (Eplerenone or Inspra).tw.
136. Eplerenone.rn.
137. exp Adrenergic Antagonists/
138. ((Adrenergic or alpha-adrenergic or beta-adrenergic) adj3 (block* or alpha-block* or beta-block* or antagonist* or alpha-antagonist* or beta-antagonist*)).tw.
139. ((alpha1 or "alpha-1" or alpha2 or "alpha-2" or beta or beta1 or "beta-1" or beta2 or "beta-2" or beta3 or "beta-3") adj2 (block* or antagonist*)).tw.
140. (adrenolytic* or anti-adrenergic* or antiadrenergic*).tw.
141. exp Phenoxybenzamine/
142. (Phenoxybenzamine or Bensylyt or Benzylyt or Dibenylene or Dibenyline or Dibenziran or Dibenzylin or Dibenzyline or Dibenzyran or Fenossibenzamina or Fenoxibenzamina or Phenoxybenzaminum).tw.
143. 59-96-1.rn.
144. exp Phentolamine/
145. (Phentolamine or Dibasin or Fentolamin or Phentolaminum or Regitine or Regityn or Rogitine or "Z-Max").tw.
146. 50-60-2.rn.
147. exp Tolazoline/
148. (Tolazoline or Artonil or Benzalolin or Benzazoline or Benzidazol or Benzolin or Benzylimidazoline or Dilatol ASI or Divascol or Imidalin or Kasimid or Lambril or Olitensol or Peripherine or Phenylmethylimidazoline or Prefaxil or Pridazole or Priscol or Priscoline or Tolazolin or Tolazolinum or Vasimid or Vasodil or Vasodilatan).tw.
149. 59-98-3.rn.
150. (Alfuzosin or Alfetim or Afusozine or Alphuzosine or Alfuzosinum or Benestan or Urion or UroXatral or Xatral).tw.
151. 81403-80-7.rn.

152. exp Prazosin/
153. (Prazosin or Furazosin or Minipress or Pratsiol or Prazosinum).tw.
154. 19216-56-9.rn.
155. exp Doxazosin/
156. (Doxazosin or Alfamedin or Apo-Doxazosin or Cardular or Cardura or Carduran or Carduran Neo or Diblocin or Doxa-Puren or Doxacor or Doxagamma or Doxamax or Doxatensa or DoxaUro or Doxazomerck or Doxazosine or Doxazosinum or Gen-Doxazosin or Jutalar or MTW-Doxazosin or Novo-Doxazosin or Progandol Neo or Uriduct or Zoxan).tw.
157. 74191-85-8.rn.
158. (Tamsulosin or Flomax or Tamsulosine or Tamsulosinum).tw.
159. 106133-20-4.rn.
160. (Terazosin or Adecur or Apo-Terazosin or Blavin or Deflox or Dysalfa or Flotrin or Flumarc or Fosfomic or Heitrin or Hytrin or Hytrine or Magnurol or Novo-Terazosin or Nu-Terazosin or Sutif or Tazusin or Terazoflo or Vasomet or Zayasel).tw.
161. 63590-64-7.rn.
162. (Atipamezole or Antisedan or Atipamezol or Atipamezolum).tw.
163. 104054-27-5.rn.
164. exp Idazoxan/
165. (Idazoxan or Idazoxanum).tw.
166. 79944-58-4.rn.
167. exp Yohimbine/
168. (Yohimbine or Aphrosol or Aphrodine or Aphrodyne or Corynine or Corynanthine or Pluriviron or Quebrachin or Quebrachine or Rauhimbine or Rauwolscine or Yocon or Yohimbin or Yohimex).tw.
169. 146-48-5.rn.
170. (Carvedilol or Carvedilolum or Coreg or Coropres or Dilatrend or Eucardic or Kredex or Querto).tw.
171. 72956-09-3.rn.
172. exp Labetalol/
173. (Labetalol or Albetol or Apo-Labetalol or Dilevalol or Dilevalolum or Labetolol or Normodyne or Presolol or Trandate).tw.
174. 36894-69-6.rn.
175. exp Alprenolol/
176. (Alprenolol or Alfeprol or Alpheprol or Alprenololum or Aptin or Aptin-Duriles or Aptina or Aptine).tw.
177. 13655-52-2.rn.
178. (Bucindolol or Bucindololum).tw.
179. Bucindolol.rn.
180. exp Carteolol/
181. (Carteolol or Carteololum).tw.
182. 51781-06-7.rn.
183. exp Nadolol/
184. (Nadolol or Anabet or Corgard or Corzide or Nadololum or Solgol).tw.
185. 42200-33-9.rn.
186. exp Oxprenolol/
187. (Oxprenolol or Coretal or Koretal or Oxprenololum or Slow Trasicor or Tevacor or Trasicor).tw.
188. 6452-71-7.rn.
189. exp Penbutolol/
190. (Penbutolol or Betapressin).tw.
191. 36507-48-9.rn.
192. exp Pindolol/
193. (Pindolol or Betapindol or "Blocklin L" or Calvisken or Carvisken or Decreten or Durapindol or Glauco-Viskin or Pectobloc or Pinbetol or Pindololum or Prinodolol or Pynastin or Visken).tw.
194. 13523-86-9.rn.
195. exp Propranolol/

196. (Propranolol or Anaprilin or Anapriline or Avlocardyl or Betadren or Betalong or beta-Propranolol or Corpendol or Dexpropranolol or Dociton or Euprovasin or Inderal or Obsidan or Obzidan or Propanix or Propranololum or Reducor or Sawatal or Sumial or Rexigen).tw.
197. 525-66-6.rn.
198. exp Sotalol/
199. (Sotalol or Darob or Sotalolum or beta-Cardone).tw.
200. 3930-20-9.rn.
201. exp Timolol/
202. (Timolol or Blocadren or Timacar).tw.
203. 26839-75-8.rn.
204. Eucommia bark$1.tw.
205. exp Atenolol/
206. (Atenolol or Tenormin or Tenormine).tw.
207. 29122-68-7.rn.
208. exp Betaxolol/
209. (Betaxolol or Betaxololum).tw.
210. 63659-18-7.rn.
211. exp Bisoprolol/
212. (Bisoprolol or Concor).tw.
213. 66722-44-9.rn.
214. exp Celiprolol/
215. (Celiprolol or Celiprololum or Selectol).tw.
216. 56980-93-9.rn.
217. Esmolol.tw.
218. Esmolol.rn.
219. exp Metoprolol/
220. (Metoprolol or Beatrolol or Beloc-Duriles or Betaloc or Betalok or Corvitol or Lopressor or Meijoprolol or Metohexal or Metoprololum or Metrol or Minax or Neobloc or Preblok or Presolol or Selokeen or Seloken or Spesicor or Spesikor or Toprol).tw.
221. 37350-58-6.rn.
222. (Nebivolol or Bystolic or Lobivon or Nebilet or Nobiten or Silostar or Vasoxen).tw.
223. Nebivolol.rn.
224. exp Angiotensin Receptor Antagonists/
225. (angiotensin adj3 (antagonist* or block*)).tw.
226. (Sartan or Sartans).tw.
227. ARBS.tw.
228. exp Losartan/
229. (Losartan or Cozaar or Losartan Monopotassium Salt or Losartan Potassium).tw.
230. 114798-26-4.rn.
231. Candesartan.tw.
232. 139481-59-7.rn.
233. (Valsartan or Diovan or Kalpress or Miten or Nisis or Provas or Tareg or Vals or Valtan or Valzaar).tw.
234. 137862-53-4.rn.
235. (Irbesartan or Aprovel or Avapro or Karvea).tw.
236. 138402-11-6.rn.
237. (Telmisartan or Kinzalmono or Micardis or Pritor).tw.
238. 144701-48-4.rn.
239. (Eprosartan or Teveten).tw.
240. 133040-01-4.rn.
241. (Benicar or Olmesartan or Omesartan or Olmetec or Votum).tw.
242. 144689-24-7.rn.
243. Azilsartan.tw.

244. Azilsartan.rn.
245. exp Hydralazine/
246. (Hydralazine or Apresoline or Apressin or Apressoline or Aprezolin or Hydrallazin or Hydrazinophthalazine or Nepresol).tw.
247. 86-54-4.rn.
248. (Dihydralazine or Depressan or Dihydrallazine or Dihydrazinophthalazin or Hypopresol or Nepresol or Nepresolin or Nepressol or Ophthazin or Tonolysin).tw.
249. 484-23-1.rn.
250. exp Minoxidil/
251. (Minoxidil or Alopexil or Alostil or Loniten or Lonolox or Mintop or Normoxidil or Prexidil or Regaine or Rogaine or Theroxidil or Tricoxidil).tw.
252. 38304-91-5.rn.
253. (Aliskiren or Tekturna or Enviage or Rasilez or Riprazo or Sprimeo).tw.
254. Aliskiren.rn.
255. exp Renin/ai [antagonists & inhibitors]
256. Clonidine/
257. (Clonidine or Adesipress or Catapres$3 or (Catapres adj TTS*) or Chlophazolin or Clofelin or Clofenil or Clopheline or Dixarit or Duraclon or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "Nexiclon XR").tw.
258. exp Antihypertensive Agents/
259. (antihypertensive* or anti-hypertensive*).tw.
260. (minizide or polypress).tw.
261. (Polythiazide adj3 Prazosin).tw.
262. 84057-89-6.rn.
263. (Enduronyl or Enduron-deserpidine).tw.
264. (Deserpidine adj3 methyclothiazide).tw.
265. 8057-21-4.rn.
266. "Diutensen-R".tw.
267. (Reserpine adj3 methyclothiazide).tw.
268. or/8-267
269. 7 and 268
270. randomized controlled trial.pt.
271. exp Randomized Controlled Trials as Topic/
272. exp Random Allocation/
273. exp Double-Blind Method/
274. exp Single-Blind Method/
275. exp Placebos/
276. (random* or RCT$1 or placebo*).tw.
277. ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
278. or/270-277
279. Controlled clinical trial.pt.
280. exp Controlled Clinical Trials as Topic/
281. exp Control Groups/
282. (controlled clinical trial* or controlled trial*).tw.
283. (control* adj ("before and after" or "before-after") adj (stud$3 or trial$1)).tw.
284. or/279-283
285. 278 or 284
286. 269 and 285
287. limit 286 to human
288. (in process or publisher or pubmed-not-medline or in-data-review).st.
289. 286 and 288 290. 287 or 289
291. (comment or editorial or interview or letter or news).pt.
292. 290 not 291

Appendix 2: Study Characteristics

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
MRC (Medical Research Council); (1992)[25]; n=4396	70.3 (NR); 41.7% ; NR	Moderate, severe	184.7 (NR); 91	No acute conditions; majority with high BMI	None	NR	Moderate/high risk; older adults 65-74 y, Baseline SBP=183-186 mmHg and high BMI
STOP-Hypertension; (1991)[26]; n=1627	75.7 (3.7); 37%; white	Moderate	Supine 195 (14); standing 188 (17); Supine 102 (7), standing 104 (9)	No acute conditions; very low % with chronic cerebral events and coronary syndromes	52.5	NR	Moderate/high risk; Elderly patients age 70-84y, SBP/DBP ≥180/90 or DBP ≥105 mmHg irrespective of SBP, high BMI
SHEP; (1991)[27]; n=4736	71.6 (6.7); 43.2%; white	Severe	170.3 (9.4); 76.6 (9.7)	Less than 20% with DM; low % with previous CVD events, raised FBG, chronic cerebral events or coronary syndromes. Renal dysfunction excluded.	33.3	NR	Moderate/high risk; Elderly ≥ 60y, high isolated SBP/DBP 160-219/90 mmHg
SHEP-PS (pilot study); (1989)[28]; n=551	72.1 (NR); 37%; white	Moderate/ Severe	172 (NR); 75 (NR)	Low % with previous CVD events, chronic cerebral events, cerebrovascular events, acute coronary syndrome, PAD. Renal dysfunction excluded.	47	3% on lipid-lowering agents; 26% taking aspirin at least 4 times per week; 2% on digitalis (no one in placebo group took digitalis)	Moderate/high risk; Elderly (age >60y); SBP 160-239 mmHg, DBP < 90 mmHg
MAPHY; (1988); n=3234	52.6 (6.5); 100%; white	Moderate	166.8 (17); 107.5 (6)	DM, previous stroke, MI, angina pectoris excluded	None	NR	Lesser risk; Age < 55y, excluded patients with history of previous coronary diseases
HAPPY; (1987)[29]; n=6569	NR; 100%; White	Moderate	166 (19); 107 (7)	DM, gout, cirrhosis, and certain previous CVD events excluded	NR	NR	Lower risk; Age < 55y, excluded patients with history of previous CVD diseases (according to authors: 47% of patients low risk and 25% moderate risk based on BP, cholesterol and smoking)
Coope, J; (1986)[30]; n=884	68.8 (5.1); 31%; NR	NR	196.2 (15.8); 99 (11.9)	Acute cerebrovascular events and cases of DM requiring meds excluded	None	NR	Moderate/high risk; Elderly age 60-79y, SBP baseline =196, excluded SBP/DBP > 280/120 mmHg
Berglund, G; (1986)[31]; n=106	NR; 100%; NR	Mild-moderate	182 (12.50; 114 (9.7)	DM excluded	None	NR	Moderate/high risk; <55y, but SBP=182 (excluded diabetics but not other CDV comorbidities

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
IPPPSH (The international Prospective Primary Prevention Study in Hypertension); (1985)[32]; n=6357	52.2 (6.5); 50.3%; NR	Moderate	173.6 (18.1); 107.5 (5.8)	DM and majority of co-morbidities excluded	40	NR	Lower risk; <55y, excluded major CDV comorbidities; Uncomplicated HTN
MRC; (1985)[33]; n=17354	52 (7.5); 52%; NR	Mild	161 (16.5); 98 (6)	DM, gout, and important CVD events excluded	None	NR	Lower risk; <55y, SBP<165, excluded important CDV
Veterans Administration Cooperative Study Group on Antihypertensive Agents; (1982)[34]; n=683	50 (NR); Mix (NR)%; white	NR	145.8 (NR; 101.6 (NR)	NR	NR	NR	Lower risk; <55y, DBP 95-114 mmHg, SBP≤ 145, not reported
Sprackling, ME; (1981)[35]; n=123	80.5 (8.4); 25.8%; NR	NR	193.9 (24.9); 107.6 (12.0)	12% with cerebrovascular disease. Less than 10% with cardiovascular disease.	5	12.5% taking "other" meds	Moderate/high risk; Elderly (age 80y), SBP=194, not all excluded CDV (<10%)
Helgeland, A; (1980)[36]; n=785	45.2 (2.9); 100%; white	Mild	156 (7.3); 97 (7.0)	All important CVD events excluded	None	NR	Lower risk; <50y, without organ damage, excluded important CVD, SBP=156
The Australian National Blood Pressure Study; (1980)[37]; n=3427	50.5 (8.9); 0.633%; white	Mild	157.1 (14.5); 100.5 (4.0)	DM and previous CVD events excluded. Very low % with acute coronary syndrome.	NR	NR	Lower risk; <55y, DBP 90-114 mmHg, "free of evidence of CVD, SBP=157
VA-NHLBI ; (1978)[38]; n=1002	NR; % NR%; NR	Mild	NR; NR	NR	NR	NR	Lower risk; Age range 21-50y, no cardiovascular renal complications, mild uncomplicated HTN (some normotensive)

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
McFate, S; (1977)[39]; n=422	44 (NR); 80%; white	Mild to moderate	147.9 (SEM 14.7); 99.3 (SEM 7.6)	Majority of conditions excluded. Less than 20% with high cholesterol (>260 mg/100 mL) and LVH. Less than 10% with gout.	41	NR	Lower risk; age 21-55y (mean = 44), SBP=148; exclusions: DM, renal insufficiency, hypercholesterolemia, abnormal ECG, previous coronary diseases, HF, thrombosis ,etc.
Veterans Administration Cooperative Study Group on Antihypertensive Agents; (1970)[40]; n=380	51.3 (NR); 100%; white	Mild to moderate	163.6 (NR); 104.2 (NR)	Renal failure, previous cerebral or subarachnoid hemorrhage, and chronic+acute cerebral events excluded. Less than 20% with LVH.	NR	NR	Lower risk; Age<55y, DBP 90-129 mmHg, exclusions of major cardiovascular or renal comorbidities.,
Veterans Administration Cooperative study - VA I; (1967)[41]; n=143	50.7 (9.7); 100%; African-American/Black	Mild to moderate	186.2 (16.3); 121.1 (4.9)	9% with DM, 32% with LVH, 30% with cardiac symptoms, 8% with previous cardiac thrombosis. Previous cerebral or subarachnoid hemorrhage, renal failure, chronic cerebral events, and uncontrolled CHF excluded.	NR	NR	Moderate/high risk; DBP 90-129 mmHg, severity evaluated in five categories: DBP, and the degree of clinically detectable hypertensive damage in the optic fundi, the brain, heart and kidney. Patients with severity of 16 or above (severe damage) were excluded.
HYVET; (2008)[42]; n=3845	83.6 (3.2); 39.5%; NR	NR	173 (8.5); 90.8 (8.5)	7% with DM. Subjects with high serum Creatinine levels and overt heart failure requiring tx with antihypertensives excluded.	60	NR	Moderate/high risk; Elderly (>80y), mean SBP=173 mmHg, some of them presented comorbidities (acute MI=3.1%, DM=7%, CVD=12%)
AASK; (2006)[43]; n=1094	55 (11.0); 61%; African-American/Black	NR	150 (24); 96 (14)	DM, CHF excluded. All had renal dysfunction. 52% with history of heart disease and 38% with LVH.	97.3	NR	Moderate/high risk: age 18-70y, all patients with CKD, 52% with history of CVD

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
ASCOT-BPLA; (2005)[43]; n=19342	63 (8.5); 77%; white	NR	164 (18.05); 94.7 (10.4)	27% with DM, 11% with stroke/TIA, 22% LVH, 6% PAD, 23% ECG abnormalities. Renal dysfunction, chronic coronary syndromes, and fasting triglyceride levels >4.5mmol/L excluded.	81	19% taking aspirin; 10.5% taking lipid lowering meds; No difference between groups	Moderate/high risk; Age=63y; SBP=164 mmHg; patients with HTN had at least 3 other cardiovascular risk factors
VALUE; (2004)[45]; n=15313	67.2 (8.1); 57.8%; white	NR	154.7 (19.0); 87.5 (10.8)	34% DM, 20% previous CVD events, 13.9% PAD, 46% coronary heart disease, 12% LVH	92.4	46.5% taking statins; 72.9% taking aspirin; difference between groups not reported	Moderate/high risk; > 50y; combinations of cardiovascular risk factors (DM, current smoking, LVH, proteinuria, raised serum Creatinine), and CVD
INVEST; (2003)[46]; n=22576	66.1 (9.8); 47.9%; White	Mild	150.9 (19.2); 87.2 (11.8)	28% DM, 32% history of MI, 67% angina pectoris, 56% hypercholesterolemia, 22% LVH, 27% previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty, 12% peripheral vascular disease, and 5% with stroke, heart failure, or acute cerebral events. Very low % with renal dysfunction	86.6	36.7% taking lipid lowering drugs; 56.7% taking antiplatelets; 18.1% on hormone replacement; 17.8% on other NSAIDs; 22.5% on antidiabetic meds, 36.7% on any lipid-lowering agent, 36.0% taking nitrates, 6.9% taking potassium supplement. No difference between groups	Moderate/high risk; HTN patients with CAD; as inclusion criteria; > 50y, with diagnosis of CAD (at least one major CVD)
INVEST; (2010); n=6668 (subgroup age 50-60 years)	54.6 (2.8); 49.7%; White	NR	NR; NR	26% with DM or history of MI, 54% dyslipidemia, 21% LVH, 9% peripheral vascular disease, 10.5% previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty, <5% with stroke/TIA or heart failure, very low % with renal dysfunction	NR	32.5% taking lipid lowering meds, 50.1% taking antiplatelets drugs. Difference between groups unclear	

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
INVEST; (2010); n=7602 (subgroup age 60-70 years)	64.6 (2.9); 49.7%; white	NR	NR; NR	32% with DM or history of MI, 58% dyslipidemia, 22% LVH, 10.9% peripheral vascular disease, 16% previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty, 5-7% heart failure or stroke/TIA. Very low % with renal dysfunction.	NR	39.1% on unspecified lipid-lowering drugs; 59.5% on unspecified antiplatelet drugs. Difference between groups unclear	
INVEST; (2010); n=6126 (subgroup age 70-80 years)	74.0 (2.8); 46.8%; white	NR	NR; NR	30% DM, 36% history of MI, 59% dyslipidemia, 22% LVH, 15% peripheral vascular disease, 21% previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty, <10% heart failure or stroke/TIA. Very low % with renal dysfunction.	NR	41.8% unspecified lipid-lowering drugs; 61.1% on unspecified antiplatelet drugs. Difference between groups unclear.	
INVEST; (2010); n=2180 (subgroup age ≥ 80 years)	83.8 (3.5); 38.7%; white	NR	NR; NR	23% DM, 37% history of MI, 46% dyslipidemia, 24% LVH, 19% PVD, 16.7% previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty, 10% with heart failure or stroke/TIA. Very low % with renal failure.	NR	27.2% on unspecified lipid-lowering drugs; 54.5% taking unspecified antiplatelet drugs. Difference between groups unclear.	
HYVET; (2003)[48]; n=1283	83.8 (3.0); 36.5%; NR	NR	181.5 (11.3); 99.6 (3.4)	Less than 5% with chronic cerebral events or acute coronary syndromes	47.9	NR	Moderate/high risk; age >80y, SBP=181 mmHg,
SHELL; (2003)[49]; n=1882	72.4 (7.5); 38%; NR	Moderate/Severe	178.1 (10.2); 86.8 (5.7)	13% with DM, 31% with history of CVD, and almost half with abnormal ECG	52	NR	Moderate/high risk; age ≥ 60 , mean isolated SBP=178 mmHg

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
SCOPE; (2003)[50]; n=4964	76.4 (NR); 35.5%; NR	NR	166.3; 90.3	12% with DM, 8% with history of previous CVD events, less than 5% with chronic cerebral events or acute coronary syndromes	52.7	9.4% on statins; 24.8% on aspirin; 9.9% on psychopharmacological drugs. Difference between groups unclear. 26% intervention vs. 18% placebo group took hydrochlorothiazide at baseline, carried through trial	Moderate/high risk; Elderly age70-89y, isolated SBP=160-179 mmHg; cardiovascular risk: medium (67%), high or very high (32.5%)
ALLHAT; (2002)[51]; n=17515 (subgroup without DM)	NR; 55.4%; NR	Mix	146.1 (15.7); 84.7 (10)	DM excluded. 27% with history of MI or stroke, 25% with LVH, 15% with previous coronary artery bypass graft surgery or percutaneous transluminal angioplasty. Co-morbidities not clearly reported.	89	26.3 on pravastatin trial, but others could be on statins outside of the companion trial (probably more were taking statins off-trial); Data on aspirin only available for complete trial groups - not the non-diabetes subgroup; 89% on previous antihypertensive tx. Difference between groups unclear.	Moderate/high risk; age >55y, at least one CHD risk factors (MI, stroke, LVH, smoking, HDL <35 mg/dL, or documented other atherosclerotic CVD)
ELSA; (2002)[52]; n=2334	56 (7.5); 54.8%; White	Mix	163.5 (12.3); 87.9 (9.3)	NR	63.3	NR	Moderate/high risk; Age 45-75, SBP/DBP 150-210/ 95-115 mmHg,, smoking 18-22%, , asymptomatic carotid atherosclerosis (>40%)
LIFE; (2002)[53]; n=9222	66.9 (7.0); 46%; Mix (92% White)	Mix	174.4 (14.3); 97.8 (8.9)	13% DM, 29% with high BMI, 18% with dyslipidemia, 16% CHD, <10% with stroke/TIA, PVD, CVD, CHF. All with LVH. Renal dysfunction excluded.	71.1 receiving treatment within 6 months before randomization	7.1% on statins (approx 6% listed as prior use in NDA report); 21.0% on aspirin (approx 34% listed as prior use in NDA); Anti-diabetics (6.6%); acid-lowering drugs (5.2%), thyroxine (5.1%), nitrates (5.0%), digoxin (3.0%), warfarin (1.4%). Women on HRT (18%). No difference between groups.	Moderate/high risk; age 55-80y, SBP/DBP 160-200/95-115 mmHg, LVH ascertained by ECG

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
LIFE; (2004); n=533	65 (NR); 54%; **African-American/Black**	NR	172 (NR); NR	25% DM, 12% with prior angina, <10% with MI, heart failure, or stroke	Mixed (no data)	44% on aspirin. No difference between groups.	_
LIFE; (2004); n=8660	NR; Mix (NR)%; Majority**White**	NR	NR; NR	NR	Mixed (no data)	NR	_
LIFE; (2008); n=4963 (subgroup all female)	67.7 (7.0); **0%;** majority White	NR	175.3 (14.1); 97.1 (8.9)	13% DM, 3% high BMI (obese), 20% dyslipidemia, 13% CHD, <10% stroke/TIA, CVD, CHF, PAD, PVD. All with LVH. Renal dysfunction excluded.	Mixed (no data)	NR	_
LIFE; (2008); n=4230 (subgroup all male)	66.1 (6.9); **100%;** majority White	NR	173.3 (14.5); 98.6 (8.8)	13% DM, 2% high BMI (obese), 16% dyslipidemia, 20% CHD, <10% stroke/TIA, PVD, CVD, CHF, PAD. All with LVH. Renal dysfunction excluded.	Mixed (no data)	NR	_
INSIGHT; (2000)[54]; n=6575	65 (6.5); 46.3%; White	NR	173 (14); 99 (8)	21% DM, 52% hypercholesterolemia, 11% LVH and low % of subjects with proteinuria, previous CVD, acute coronary syndromes, or PVD,	87	NR	Moderate/high risk; age 55-80y SBP/DBP≥ 150/95 or SBP≥160 mmHg, at least one additional CVD risk factors (hypercholesterolaemia, smoking, family history of MI, LVH, CHD, left-ventricular strain, PVD, proteinuria)
NORDIL; (2000)[55]; n=10881	60.4 (6.5); 48.6%; NR	Isolated systolic HTN	173.5 (17.6); 105.7 (5.3)	Low % with DM, previous CVD events, renal dysfunction, chronic cerebral events, cerebrovascular events, chronic coronary syndromes	43.7	NR	Moderate/high risk; age55-74y, DBP≥ 100 mmHg, 50% untreated,
STOP-2; (1999)[56]; n=6614	76 (NR); 33%; NR	Mix	194 supine; 187 standing; 98 supine; 101 standing	Low % with DM, previous CVD events, chronic cerebral events, acute coronary syndromes, ischemic heart disease, CHF	NR	NR	Moderate/high risk; age 70-84, SBP/DBP≥180/105 mmHg or both

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
NICS-EH; (1999)[57]; n=414	69.8 (6.5); 33% [significantly higher proportion of men in the nicardipine group]%; NR	Mix	172.3 (11.9); 93.8 (10.2)	DM and a majority of conditions excluded, 30% LVH	60.5 using hypertensive med at recruitment	Proportion on statins and aspirin NR. All other hypertensive medications were prohibited.	Moderate/high risk; age≥60y, SBP/DBP 160-220/<115 mmHg (after 4 weeks placebo), no cardiovascular conditions
MIDAS; (1996)[58]; n=883	58.5 (8.5); 77.8%; white	NR	149.7 (16.6); 96.5 (5.1)	Renal dysfunction, raised FBG, and hyperlipidemia excluded. Very low % with previous CVD events.	76.4	NR	Moderate/high risk; age ≥40y, DBP 90-115 mmHg, presence of IMT in the carotid artery with no evidence of plaque complications
PATS; (1995)[59]; n=5665	60 (8.0); 72%; Asian-100	Moderate	154 (24); 93 (13)	DM excluded. All had previous CVD event. 87% with acute cerebral events, 12% with cerebrovascular events.	Mixed (no data)	NR	Moderate/high risk; all with history of TIA or minor stroke or history of major stroke but not severely disabled irrespective of BP
CASTLE; (1994)[60]; n=351	73.4 (5.1); 51%; white	Moderate	177.6 (21.5); 96.6 (11.3)	Low % with DM, previous CVD events, acute coronary syndromes	NR	NR	Moderate/high risk; Elderly (73y), SBP 177 mmHg
EWPHE; (1985)[61]; n=840	72 (8.0); 30.2%; NR	Mild to moderate	182 (16); 101 (7)	NR	NR	NR	Moderate/high risk; age≥60y, SBP/DBP 160-230/90-119 mmHg
VHAS; (1997)[62]; n=1414	54.2 (7.0); 49%; NR	Mild to moderate	169.0 (10.5); 102.3 (5.1)	DM (Type 1/uncontrolled Type II), severe PAD, familial dyslipidemia, and recent (<6 months) CVD events/acute coronary syndromes excluded. 20% with high BMI.	NR	2.3% lipid-lowering drugs; 2.1% anti-platelet drugs; 3.6% hypoglycemic drugs. No difference between groups.	Lower risk; age 40-65y, SBP/DBP≥ 160/95 mmHg, excluded major CVD
TRANSCEND (and ONTARGET); (2008)[63]; n=4528	66.9 (7.3); 57%; white	NR	140.9 (16.6); 82 (10.1)	36% DM, 22% chronic cerebral events, 47% with history of angina or MI, 10-26% with LVH, PAD, CAD grafting, angioplasty. Majority with previous CVD events, CAD.	NR	55% on statins. 75% on aspirin. 79.5% on antiplatelet agents. 10.5% on Clopidogrel or ticlopidine. No difference between groups.	Moderate/high risk; established coronary artery, peripheral artery or cerebrovascular disease, or DM with end-organ damage, intolerant of ACE-i, excluded SBP > 160 mmHg

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
STAR (the Study of Trandolapril/Verapamil SR and Insulin Resistance); (2006)[64]; n=276	56.5 (9.9); 48.7%; white	NR	146.01 (16.1); 87.3 (9.7)	Diabetics taking more than 2 antihypertensives excluded. All subjects had impaired glucose tolerance.	NR	NR	Lower risk; Age <55y (>21y), SBP <140 on two antihypertensive medications or ≥ 130 <160 mmHg on monotherapy, 100% metabolic syndrome, but not reported comorbidities
FEVER; (2005)[65]; n=9800	61.5 (7.1); 61%; Asian	Mix	154.3 (12.1); 91.2 (7.1)	13% DM, 15% with history of stroke or with chronic cerebral events, 24% elevated serum cholesterol, 41% with high BMI, 11% LVH, very low % with PAD and history of MI. Renal dysfunction, raised FBG, and acute cerebral events excluded.	88.7	0.74% on statins; 11% on aspirin; 7.0% on anticoagulants. No difference between groups.	Moderate/high risk; age 50-79y, or age < 60 with, at least two CV risk factors (MI, stroke, CHD PAD, TIA), SBP ≤210 /DBP < 115 mmHg if treated or SBP/DBP 160-210/95-115 untreated
FEVER; (2011); n=5920 (male subgroup)	61.9 (7.1); 100%; Asian	NR	154.1 (12.3); 91.7 (6.9)	Approx. 10% with DM or LVH. 35% current or previous CVD. Renal dysfunction excluded.	Mixed (no data)	NR	_
FEVER; (2011); n=3791 (female subgroup)	60.9 (6.8); 0%; Asian	NR	154.7 (12.1); 90.4 (7.8)	15% with DM, 13% LVH, 54% with current or previous CVD. Renal dysfunction excluded.	Mixed (no data)	NR	_
FEVER; (2011); n=3179 (age >65 y)	69.5 (3.3); 65.5%; Asian	NR	156.3 (11.9); 89.1 (8.1)	13% DM, 10% LVH, 30% with current or previous CVD. Renal dysfunction excluded.	Mixed (no data)	NR	_
FEVER; (2011); n=6532 (age≤65 y)	57.6 (4.7); 58.8%; Asian	NR	153.4 (12.3); 92.2 (6.7)	13% DM, 12% with LVH, 42% with current or previous CVD. Renal dysfunction excluded.	Mixed (no data)	NR	_
PHYLLIS-Zanchetti, A; (2004)[66]; n=508	58.4 (6.7); 40.3%; NR	NR	159.8 (8.9); 98.3 (4.2)	NR	Mixed (no data)	50% on statins	Moderate/high risk; age<55, SBP 150-210/95-115 mmHg, hypercholesterolemic patients with asymptomatic atherosclerosis

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
Wing, LMH; (2003)[67]; n=6083	71.9 (NR); 49%; NR	Mix	168 13); 91 (8)	Low % (<10) DM, previous CVD events, cerebrovascular events, coronary syndromes. 37% with hypercholesterolemia.	62	13% were receiving lipid-lowering drugs at baseline. No difference between groups.	Moderate/high risk; age 65-84y, SBP ≥160 mm Hg or an average DBP ≥90 mm Hg (if SBP ≥140 mm Hg), no history of CVD in past 6 months,
PROGRESS; (2001)[68]; n=2916 with HTN	64 (10.0); 70%; Asian	Mild to moderate	for those with HTN: 159 (NR); 94 (NR)	13% DM, 11% cerebral hemorrhage, 4.5% unknown stroke, 71% ischemic stroke, 22% TIA amaurosis fugax	50	NR	Moderate/high risk; all with previous stroke or TIA, no BP entry criteria
SYS-EUR; (2000)[69]; n=4695	70.2 (6.7); 33.2 in pre-randomized sample NR otherwise%; NR	Moderate to Severe	sitting 173.8 (9.99); standing 168.9 (12.3); sitting 85.5 (5.8), standing 87.3 (7.7)	All severe comorbidities were excluded. 30% with previous CVD event, 12% MI, 9% CHD, 44% LVH, very low % with symptoms of cerebrovascular disease. Renal dysfunction, acute cerebral events, and acute coronary syndrome excluded	43	NR	Moderate/high risk; age ≥60y, SBP/DBP 160-219/<95 mmHg
AIPRI; (1996)[70]; n=583 (82% with HTN)	51 (12.5); 72%; NR	NR	143 (17); 87.5 (9)	Type 1 DM, CHF excluded. All with renal insufficiency.	78	Antihypertensive therapy used by 78% at baseline, adjusted as necessary during study to maintain target DBP. If pts were previously on ACEi, this was replaced with an alternative.	Moderate/high risk; age 18-70y, All with renal insufficiency (60% moderate), no BP criteria
ALPINE; (2003)[71]; n=393	55.0 (9.5); 52.5%; white	Mild to moderate	154.9; 13.4	DM excluded. Those with hyperlipidemia requiring tx excluded.	5.6	NR	Lower risk; Age<55y, SBP 140–179 mmHg and/or DBP 90–104 mmHg, exclusion of severe comorbidities

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
The GISEN Group; (1997); n=352 (87% HTN)	49.4 (13.6); 79%; NR	NR	149 (17.6); 91.9 (11.3)	All with renal dysfunction. Insulin dependent DM excluded; type 2 NR.	77% on treatment at study inception	NR	Moderate/high risk; <55y, SBP/DBP > 140/90 mmHg all chronic nephropathies (64% glomerular), excluded CVD
Kumagai, H; (2000)[73]; n=72	58.5 (9.6); 57%; Asian	NR	163.8 (9.7); 99.4 (6.9)	10% with DM not included in analysis. MI, HF excluded. All with renal dysfunction.	NR	NR	Moderate/high risk; >55y, SBP/DBP > 140/90 mmHg, all with renal dysfunction
Tedesco, MA; (1999)[74]; n=69	55 (11.1); 52%; NR	Mild to moderate	135 (11); 84 (6)	Renal dysfunction, recent MI and stroke excluded.	30 no previous tx; 59 continuous treatment; 11 discontinuous tx	NR	Lower risk; age 30-73y, DBP 90-115 mmHg, excluded cardiorenal conditions
Perez-Stable, EJ; (2000)[75]; n=312	45.5 (6.7); 66.3%; white	Mild	140.5 (11.5); 96.0 (4.0)	Stroke and renal dysfunction excluded. Very low % with DM and angina. None with history of MI, or acute/chronic cerebral events, cerebrovascular events.	43	NR	Lower risk; 22-59y, DBP 90-104 mmHg, excluded cardiorenal conditions
Neutel, JM; (1999)[76]; n=578	53.5 (MR); 75%; White	Mild to moderate	153.1 (NR); 100.7 (NR)	NR	Mixed (no data)	NR	Lower risk; DBP 95-114 mmHg
Schmieder, RE; (2009)[77]; n=1124	55.9 (10.9); 55%; white	Mild to moderate	154.2 (11.1); 98.9 (3.3)	11% DM, 43% with "other" metabolic syndrome. Severe renal dysfunction and recent CVD events excluded.	Mixed (no data)	79.6 took undisclosed medications (at least 1 non-study drug) along with Aliskiren, n=566; hydrochlorothiazide, n=558. (according to this, one participant crossed over from aliskiren to hydrochlorothiazide at inception/baseline)	Lower risk; age ≥18y, DBP ≥90 mm Hg and <110 mm Hg at the single-blind placebo, patients with history of severe cerebrovascular or CVD were excluded
Stanton, AV.; (2001)[78]; n=69	NR; 59%; white	NR	164.5 (18); 99.9 (9.5)	DM, hypercholesterolemia, and other systemic conditions excluded	NR	None were on lipid meds during the trial.	Lower risk; age 20-80y, SBP/or DBP 140-220/ 90-120 mmHg, Excluded DM, hypercholesterolemia, significant systemic conditions

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
T Hannedouche; (1994)[79]; n=100	51 (2.0); 53%; NR	Mild to moderate	166.5 (2.5); 102.0 (1.5)	DM excluded. All with renal dysfunction.	NR	NR	Moderate/high risk; age 18-70y, all patients with CKD
JMIC-B; (2003)[80]; n=1650	65 (6.0); 68.8%; Asian	NR	146 (19.5); 82 (11.5)	23% with DM. 42% with history of MI, 65% with history of angina pectoris, 23% hyperlipidemia. Uncontrolled DM, familial hyperlipidemia, and acute conditions (i.e. MI, unstable angina pectoris) excluded.	92	27.8% on antihyperlipidemic drugs; 54.8% on antiplatelets. Difference between groups NR.	Moderate/high risk; 65y, SBP/DBP≥160/≥95 mmHg, all had history of CVD and at least risk factors
VART; (2011)[81]; n=1021	60 (11.5); 57.2%; NR	Mild to moderate	158 (18.5); 93.5 (13)	10% with DM; very low % with history of coronary artery disease.	45.8	10% on statins; 2.4% on anticoagulants; 3% on oral hypoglycemic agents; 1% on fib rates. No difference between groups.	Moderate/high risk; age 60y, SBP=158, 10% diabetes, hyperlipidemia 28%, CHD 3.5%, smokers 3,5%
JLIGHT; (2003)[82]; n=117	56.6 (12.7); 66%; Asian	NR	156 (12.9); 93.7 (8.9)	All with renal dysfunction	None	NR	Moderate or moderate Moderate/high risk; age 20-74y, SBP/or DBP ≥140/≥90 mmHg, all had CKD and proteinuria
Black, H. R.; (2001)[83]; n=171	66 (6.8); 49%; white	Mild	149 (7.3); 83 (5.6)	NR	NR	NR	Lower risk; ≥55y, SBP/DBP 140-159/>90 mmHg, comorbidities NR
ACTION trial; (2005)[84]; n=7797	65.0 (8.9); 76%; -	Isolated systolic HTN	151.4 (13.7); 84.8 (8.6)	17% DM (unstable DM requiring insulin excluded), 26% with high BMI, 66% with elevated total cholesterol, 92% reported anginal attacks, 49% with history of MI, 15% with history of PVD (stroke, TIA, or claudication). Heart failure and major recent (within 3 months) CVD events or interventions excluded.	54	62.6% of ACTION participants on statins at baseline[117] Information for the hypertensive subgroup (group if interest) not reported, however, "Lipid-lowering treatment was either continued or started at the same time as study medication according to internationally accepted guidelines". No difference between groups in main trial (ref ID 10520). Data specific to hypertensive group not reported.	Moderate/high risk; 65y, SBP/or DBP ≥ 200/≥105 mmHg, all symptomatic stable angina, 17% diabetes, 66% hypercholesterolemia, 49% AMI

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Marin, R; (2001)[85]; n=241	54 (14.0); 59%; Hispanic	NR	156.16 (18.4); 96 (9.39)	DM, previous CVD events excluded. All with renal dysfunction.	NR	Excluded pts taking NSAIDs.	Moderate/high risk; 54y, SBP/DBP >140/90 mmHg, Excluded diabetes and previous CVD. Included primary renal disease
Chalmers, J; (2000)[86]; n=259	72.4 (5.4); 42%; NR	Mild, to moderate	170.1 (10.9); 94.7 (8.1)	Uncontrolled DM or DM requiring tx (insulin, metformin), recent (within last 6 months) CVD events, renal dysfunction, high BMI, and acute coronary syndromes requiring tx excluded.	77.9	NR	Moderate/high risk; age 65-85y, SBP/ or DBP ≥ 160-210/ or ≥95-114 mmHg, or isolated HTN (DBP < 95, SBP 160-201), excluded important comorbidities
Otterstad, JE; (1992)[87]; n=100	47 (10.0); 100%; NR	Mild/ Mild-Moderate	156 (13); 103 (5)	Renal dysfunction excluded	26	NR	Lower risk; age 20-65y (<55y), DBP 95-110 mmHg, exclusion CKD
NAVIGATOR; (2010); n=9306	63.8 (6.8); 49.3%; NR	NR	139.7 (17.4); 82.6 (10.2)	None with DM but all had impaired glucose tolerance. 12% with history of MI and 9% with angina. Majority with metabolic syndrome (84%). Very low % with history of stroke, intermittent claudication, peripheral artery stenosis, percutaneous coronary intervention, artery bypass grafting, lower limb angioplasty, or bypass surgery. Only 3% with LVH.	NR	38.4% lipid-lowering drugs. Increased to 50% by last study visit. 36.8% aspirin or other antiplatelet drug. Increased to 45.5% by last study visit. 73.2% any antihypertensive drug. By last study visit, significantly more pts in placebo group receiving any hypertensives (79.1% vs. 73.6%; p<0.001).	Moderate/high risk; Patients with impaired glucose tolerance and at least one CVD risk factor or known CVD if ≥ 55y
Takahashi, A; (2006)[89]; n=80	61 (SE 1); 58.8%; NR	NR	153 (SEM 3); 83 (SEM 2)	33% with DM. All with renal dysfunction (on haemodialysis). <10% with high BMI or hyperlipidemia. History of MI excluded.	Mixed (no data)	12.5% on aspirin; 23.8% on antidiabetic agents. No difference between groups.	Moderate/high risk; ≥35 y (61y), all patients on chronic haemodialysis, 33% DM
Hou, FF.; (2006)[90]; n=224	44.7 (15.5); 50%; Asian	NR	152. (23.15); 85.9 (10.35)	DM excluded. All with renal dysfunction.	NR	NR	Moderate/high risk; age 18-70y , SBP=152, all mild-to-moderate renal dysfunction without diabetes

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DAPHNE; (2002)[91]; n=80	59.1 (7.2); 100%; white	Mild/moderate	163.5 (16.9); 100.5 (5)	DM excluded. All with hypercholesterolemia. 10% with chronic cerebral events, 19% with chronic coronary syndrome, 78% with PAD, and 44% received surgery for PVD.	NR	NR	Moderate/high risk; age 45-70y, DBP 95-115 mmHg, smokers=49%, AMI=20%, coronary bypass=15%, stroke 7%, all hypercholesterolemia
Keane, W; (1997)[92]; n=317	48.5; 61%; white	NR	138.5 (21.9); 86.5 (10.9)	DM excluded; 100% with renal dysfunction	Mixed (no data)	NR	Lower risk; non-diabetics with some degree of renal impairment, excluded renal artery stenosis (without diagnostic criteria)
Materson, BJ; (1993)[93]; n=1292	59 (10.0); 100%; NR	Mix	152 (14); 99 (3)	NR	71	NR	Lower risk; age ≥20y, DBP 90-105 mmHg, patients with comorbidities excluded
Bremner, AD; (1997)[94]; n=501	71.8 (5.3); 44.7%; white	Mild to moderate	Sitting: 174.7 (14.9); Sitting: 102.0 (3.8)	NR	56	NR	Moderate/high risk; elderly age ≥65y, DBP 96-110 mmHg, excluded previous history of CVD
Puig JG; (1991)[95]; n=22	50.5 (9.0); 72.2%; NR	Mild to moderate	157 (13.6); 103 (8)	DM and renal dysfunction excluded	73.3	NR	Lower risk; age 37-88y, , DBP 95-110 mmHg, no significant comorbidities
Komsuoglu, B; (1989)[96]; n=80	51.6 (63.8); 47.5%; NR	NR	204 (NR), 113 (NR)	DM and previous CVD events (angina, CHF, valvar heart disease, pervious MI)	20	NR	Lower risk; 51y, DBP > 95 mmHg, excluded major comorbidities (CHF, valvar heart disease, angina, previous MI, diabetes)
Glaxo Group Research; (1991)[97]; n=553	57 (NR); 46.5%; NR	Mild to moderate	164 (NR); 102 (NR)	NR	NR	NR	Lower risk; 46y, SBP/DBP ≤200/95-115 mmHg, exclusions/comorbidities NR
REIN trial; (1999)[98]; n=152	49.7 (13.4); 0.747%; NR	Mild, moderate	143.4 (18.8); 89.2 (12.0)	DM requiring insulin, previous CVD events (acute MI or cerebrovascular accident in past 6 months) excluded. All with renal dysfunction	60.6 of Ramipril group. 71.3 of Placebo group	NR	Lower risk; age 18-70y (<55y), SBP=143, exclusions: DM, previous CVD; All had chronic nephropathy and persistent proteinuria
Yurenev, AP; (1992)[99]; n=304	45.5 (SE 0.5); Mix (NR)%; NR	Moderate, moderate to severe	168.5 (SEM 1.7); 105.9 (SEM 1.0)	NR	NR	NR	Moderate/high risk; <55y, SBP/DBP >160/95 mmHg different degrees of Left ventricular distrofia
Talseth, T; (1990)[100]; n=228	NR; Mix (NR)%; NR	Mild, moderate	160 (NR); 103 (NR)	NR	Mixed (no data)	NR	Lower risk; Age 18-70y, excluded patients with CVD, cerebrovascular, haematological and hepatic diseases

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
Zucchelli, P; (1995)[101]; n=120	55 (10); 57%; NR	Mild to moderate	165 (20.5); 100 (12.5)	DM excluded. All with renal dysfunction.	NR	NR	Moderate/high risk; age 18-70 y , excluded patients with reversible renal disease, systemic disease, severe cardiac or hepatic dysfunction, proteinuria (>5g/24h) and DM. All patients mild to moderate non-diabetic renal disease
LOMIR-MCT-IL; (1996)[102]; n=368	52 (7.6); 100%; NR	Mild to moderate	152.5 (13.9); 99.6 (2.9)	DM requiring insulin, recent CVD events, and elevated Creatinine levels excluded	Mixed (no data)	NR	Lower risk; <55y, DBP 95-105 mmHg, excluded patients with secondary HTN, malignant HTN, unstable angina, MI or any clinically relevant CVD or abnormal laboratory findings (e.g. liver function tests and CrS), alcohol use, mental disorder, type1 DM
MadGregor, MS; (2005)[103]; n=73	NR; 53.4%; NR	Mild	148 (20); 88 (10)	DM excluded. All with renal dysfunction.	NR	Other ACE inhibitors, angiotensin receptor antagonists and calcium channel blockers were stopped. Alterations to other antihypertensives at enrolment were at the clinician's discretion.	Moderate/high risk; age, 18-80y , DBP > 90 (or treated), All had advanced renal failure, excluded diabetic nephropathy. Other CVD comorbidities not reported.
Tepel, M; (2008)[104]; n=251	NR; 63.3%; NR	Mild to moderate	Median (25-75% percentile) 140: (128-160); 80 (70-82)	Approx. 30% with DM or CVD. Heart failure, recent MI excluded. All with renal dysfunction.	Mixed (no data)	41% of participants on lipid-lowering drugs. No differences between groups apparent within data presented (limited data available)	Moderate/high risk; age 63y, all hypertensive haemodialysis patients. 30% DM or CVD
HOPE; (2002)[105]; n=9541(n=2481 (44%) with HTN	NR; NR for subgroup%; NR	NR	136 (20); 79 (11)- NR for HTN subgroup	DM in 38% of all patients	NR	NR for HTN subgroup	Moderate/high risk; 80% with history of CAD, 11% history of stroke or TIA, 43% PAD, 38% DM, and 44% HTN (this information NR for HTN subgroup)
Heesen, WF; (2001)[106]; n=97	68.0 (NR); 48.4%; NR	NR	135.4 (12.6); 76.4 (7.3)	5% with DM	NR	NR	Lower risk; age 60-75, SPB/DBP ≥160/ < 95 mmHg, excluded cardiovascular accident, MI, stroke, CHF, cardiac arrhythmia

Summary of Main Clinical Characteristics and Assigned Risk Level of Population							
Study and Year; sample size	**Mean Age (SD); % male; ethnicity (majority)**	**Study's indicated HTN severity at baseline**	**SBP mean (SD) at baseline; DBP mean (SD) at baseline**	**Summary of Patient Co-morbidities**	**% with past use of anti-HTN agents**	**Summary of concurrent medication: Statins; Aspirin (CT-DE); NR denotes 'not reported'**	**Our preliminary risk classification (moderate/severe vs. lower risk) and Rationale**
ELVERA trial; (2001)[107]; n=166	67 (NR); 55.4%; NR	Mild to moderate	172.4 (14.5) [the value for Lisinopril group is considered to be 170 mmHg since there is an error in table 1); 92.5 (8.5)	DM and renal dysfunction excluded. Mildly obese.	None	NR	Lower risk; age 60-75y, SBP/DBP 160-220/95-115 mmHg, newly diagnosed HTN (previously untreated); exclusion of insulin dependent DM, renal disease, manifested CAD, CHF, hemodynamically significant valvular heart disease
Ihle, BU.; (1996)[108]; n=70	44.4 (NR); 51.4%; NR	NR	150 (range 110-190); 88 (69-120)	All with renal dysfunction.	19.4 vs. 41.2 took frusemide	NR	Moderate/high risk; age 18-75y All patients were non-diabetic adult with CKD. Not specifically mentioned HTN or CVD
Kamper, AL; (1992)[109]; n=70 (84% with HTN)	48.5 (NR); 52.8%; NR	NR	NR; -	All with renal dysfunction.	84.3	NR	Lower risk; age 15-75y, all progressive renal disease (regularly controlled). Excluded renal artery stenosis, cancers and other serious non-renal comorbidities
Veterans Administration Cooperative Study on Antihypertensive Agents; (1960)[110]; n=425	NR; 100%; White	Mild to moderate	161 (NR); 103 (NR)	NR	45	NR	Moderate/high risk; adults <70y, DBP > 90 mmHg, excluded MI, terminal uremia,
Veterans Administration Cooperative Study on Antihypertensive Agents; (1977)[111]; n=450	47.7 (0.8); 100%; NR	Mild to moderate	150.6 (1.5); 97.7 (0.5)	DM, elevated Creatinine levels, acute+chronic cerebrovascular events excluded.	Mixed (no data)	NR	Lower risk; Age 18-59 (mean 48), SBP=150, excluded DM, CHF, COPD, renal and cerebrovascular conditions
Perez-Stable, E (1995)[112]; n=312	45.4 (8.3); 66%; 73% White	NR	140.8 (NR; 95.7 (NR)	Insulin depended DM, coronary artery disease , and renal dysfunction were excluded.	43	NR	Lower risk; age 22-59y, DBP 90-104 mmHg, excluded CAD, valvular heart disease, renal insufficiency, cerbrovascular disease, insulin dependent Dm

Cochrane Scale Risk of Bias Evaluations of Included Studies									
Study	**Selection Bias**		**Other Sources of Bias**		**Blinding**		**Attrition Bias**	**Are reports of the study free of suggestion of selective outcome reporting?**	**Is this study free of financial conflicts of interest?**
	Adequate sequence generation?	**Allocation concealment?**	**Possible major baseline imbalance**	**Possible variables with unknown (i.e. not reported) or unclear risk of confounding**	**Blinding of Participants/ caregivers/ outcome assessors**	**Potential bias due to lack of blinding**	**Were incomplete outcome data adequately addressed?**		
MRC Working Party (1992)[25]	Unclear	Unclear	N/A	Race, concomittant medications	Yes/No/Yes	Low	Unclear	Unclear	Unclear
Dahlof, B (1991)[26]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	Yes/Unclear/Yes	Low	Low	Unclear	Unclear
SHEP Cooperative Research Group (1991)[27]	Unclear	Low	N/A	Concomittant medications, other (no adjustment for confounding; no info on other meds)	Yes/Yes/Yes (blinding not maintained throughout the trial)	Unclear	Unclear	Unclear	Unclear
Perry, HM (1989)[28]	Unclear	Low	N/A	Comorbidities (angina, carotid bruits higher in placebo group)	Yes/Yes/Unclear	Low	Unclear	Unclear	Unclear
Wikstrand, J (1988)[212]	Unclear	Unclear	N/A	Concomittant medications	No/No/Yes	High	Low	Low	Unclear
Wilhelmsen, L (1987)[29]	Unclear	Unclear	N/A	N/A		High	Low	Unclear	Low
Coope, J (1986)[30]	Low	Low	N/A	Race, concomittant medications, comorbidities	No/No/Yes	High	High	Unclear	Unclear
Berglund, G (1986)[31]	Unclear	Unclear	N/A	Age, race, concomittant medications, comorbidities (NR except for diabetes)	No/No/No	High	Unclear	Unclear	Low

The IPPPSH Collaborative Group (1985)[32]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Unclear/Yes Identical tablets, 'Double-blind'	Low	Unclear	Unclear	Unclear
MRC working party (1985)[33]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	Yes/No/Yes	Low	Low	Unclear	Unclear
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982)[34]	Unclear	Unclear	N/A	Age, gender, baseline BP, concomittant medications, comorbidities, other (baseline values not defined)	Yes/Yes/Unclear Double-blind; identical tablets	Unclear	high	Unclear	Unclear
Sprackling, ME (1981)[35]	Low	Unclear	N/A	Age, race, baseline BP, concomittant medications, comorbidities	No/No/No	High	Unclear	Unclear	Low
Helgeland, A (1980)[36]	Low	Unclear	N/A	Race	No/No/Unclear	High	Unclear	Unclear	Unclear
The Australian Therapeutic Trial in Mild Hypertension Committee (1980)[37]	Unclear	Unclear	N/A	N/A	Yes/Unclear/Yes Identica placebol ta blets	Low	Unclear	Unclear	Unclear
Perry, HM (1978)[38]	Unclear	Unclear	N/A	Age, gender, race, baseline BP, concomittant medications, comorbidities, other	Yes/Unclear/Unclear Double-blind	Unclear	Unclear	High	Unclear
The USPHS study- (1977)[39]	Unclear	Unclear	N/A	N/A	Yes/Unclear/Unclear Double-blind, identical placebo tables	Unclear	Unclear	Unclear	Unclear
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970)[40]	Low	Unclear	N/A	Concomittant medications	Yes/Yes/Yes Identical placebo	Low	Unclear	Unclear	Unclear
Smith JM, (1967)[41]	Low	Unclear	N/A	Concomittant	Yes/Yes/Yes Identical placebo	Low	Unclear	Unclear	Unclear

				medications					
Beckett, NS (2008)[42]	Unclear	Low	N/A	Race, concomittant medications	Yes/Yes/Yes	Low	Low	Low	Unclear
Norris, K (2006)[43]	Unclear	Unclear	N/A	Concomittant medications	Yes/Yes/Yes	Low	high	Low	Unclear
Dahlöf, B (2005)[44]	Low	Unclear	N/A	N/A	No/No/Yes PROBE design	High	Low	Unclear	Unclear
Julius, S (2004)[45]	Low	Low	N/A	N/A	Yes/Yes/Yes	Low	Low	Unclear	High
Pepine, CJ (2003)[46]	Low	Unclear	N/A	N/A	No/No/Yes	Low	Low	Unclear	High
Bulpitt, CJ (2003)[48]	Low	Unclear	N/A	Race, concomittant medications, comorbidities	No/No/No	High	Unclear	Unclear	Low
Malacco, E. (2003)[49]	Unclear	Unclear	N/A	Race	No/No/No	High	Unclear	Unclear	Unclear
Lithell, H (2003)[50]	Low	Low	N/A	Race	Yes/Unclear/Yes Double-blind, placebo-controlled (similar tablets)	Low	Low	High	Unclear
ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2002)[51]	Low	Low	N/A	Concomittant medications, comorbidities for the subgroup with HTN	Yes/Yes/Unclear Double-blind	Low	Unclear	High	High
Zanchetti, A (2002)[52]	Low	Low	N/A	Comorbidities	Yes/Yes/Yes	Low	Low	Unclear	High
Julius, S (2004)[53]	Low	Low	N/A	Concomittant medications (concerns from the correspondence: more patients in the losartan arm were taking diuretic vs. atenolol arm (44% vs. 38%)	Yes/Yes/Yes Triple-blind	Low	Unclear	Unclear	High

Brown, MJ (2000)[54]	Low	Unclear	N/A	Baseline BP, concomittant medications	Yes/Yes/Yes	Low	Low	Unclear	Unclear
Hansson, L (2000)[55]	Low	Low	Cross over: substantial overlap between groups, particularly with the intervention group taking diuretics and beta-blockers	Race, concomittant medications	No/No/Yes PROBE design	High	Low	Unclear	High
Hansson, L (1999)[56]	Unclear	Low	N/A	Race, concomittant medications	No/No/Yes PROBE design	Low	Low	Low	High
National Intervention Cooperative Study in Elderly Hypertensives Study Group (1999)[57]	Unclear	Unclear	Gender: notably more males in the nicardipine vs. trichlormethiazide group (40% vs. 26%)	Race, concomittant medications , comorbidities	Yes/Yes/Yes Double-blind, double-dummy	Low	Unclear	Unclear	Unclear
Borhani, NO (1996)[58]	Unclear	Unclear	N/A	Concomittant medications	Yes/Yes/Yes	Low	Unclear	Unclear	Unclear
PATS Collaboration group (1995)[59]	Unclear	Unclear	N/A	Concomittant medications	Yes/Unclear/Unclear Double-blind, placebo-controlled	Unclear	Unclear	Unclear	Unclear
Gasiglia, E (1994)[60]	Unclear	Unclear	N/A	Age, gender, race, baseline BP, concomittant medications, comorbidities	No/No/No	High	Unclear	Unclear	Unclear
Amery, A (1985)[61]	Unclear	Unclear	N/A	Race, concomittant medications	Yes/Yes/Yes Double-blind	Low	Unclear	Low	Unclear
Rosei, EA (1997)[62]	Unclear	Unclear	N/A	Race, comorbidities	Yes/Unclear/Yes Double-blind (6 months, Open (18 months)	Unclear	Unclear	Unclear	Unclear

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators (2008)[63]	Unclear	Low	N/A	Concomittant medications, comorbidities for the subgroup with HTN	Yes/Yes/Yes	Low	Low	High	Low
Bakris, G. (2006)[64]	Unclear	Unclear	N/A	Comorbidities, concomittant medications	No/No/Yes PROBE	Low	Low	Unclear	Unclear
Zhang, Y (2011)[65]	Low	Low	N/A	Comorbidities (diabetes, and stroke. Risk in the subgroups analysis since these factors were not adjusted for)	Yes/Yes/Yes	Low	Low	Unclear	Unclear
Zanchetti, A (2004)[66]	Low	Unclear	N/A	Race, concomittant medications, comorbidities, other (review other did not elaborate)	Yes/Yes/Yes	Low	Unclear	Unclear	Unclear
Wing, LMH (2003)[67]	Unclear	Unclear	N/A	N/A	No/No/Yes PROBE design	Low	Unclear	Low	Low
PROGRESS Collaborative Group (2001)[68]	Unclear	Unclear	N/A	N/A	Yes/Unclear/Unclear Double-blind	Unclear	Low	Unclear	Unclear
Staessen, JA (2000)[69]	Low	Unclear	**N/A**	Race, concomittant medications	Yes/Yes/Yes Double-blind, matching placebos	Low	Low	Low	Unclear
Maschio, G (1996)[70]	Unclear	Unclear	N/A	Race, comorbidities	Yes/Yes/Unclear Double-blind	Low	high	Unclear	Unclear
Lindholm, LH (2003)[71]	Unclear	Unclear	N/A	Concomittant medications	Yes/Unclear/Unclear Double-blind	Unclear	Low	Unclear	Unclear
The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) (1997)[72]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	Yes/Yes/Unclear Double-blind, identical placebo tablets	Low	Low	Unclear	high

Kumagai, H (2000)[73]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	No/No/No	high	High	Unclear	Unclear
Tedesco, MA (1999)[74]	Unclear	Unclear	N/A	Race, baseline BP, concomittant medications, comorbidities	Yes/Yes/Yes Double-blind	Low	Low	Unclear	Unclear
Perez-Stable, EJ (2000)[75]	Low	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Yes Matched placebo	Low	Unclear	Unclear	Low
Neutel, JM (1999)[76]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Unclear Double-blind, double-dummy	Unclear	Unclear	Unclear	Unclear
Schmieder, RE (2009)[77]	Low	Low	N/A	N/A	Yes/Yes/Unclear Double-blind	Low	High	Unclear	High
Stanton, AV. (2001)[78]	Low	Unclear	N/A	Concomittant medications, comorbidities	Yes/Unclear/Yes Double-blind	Low	Unclear	Unclear	Unclear
T Hannedouche (1994)[79]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	No/No/No Open trial	High	Unclear	Unclear	Unclear
Yoshiki YUI (2003)[80]	Low	Unclear	N/A	Concomittant medications, comorbidities	No/No/Yes PROBE design	Low	Unclear	Unclear	Low
Narumi, H (2011)[81]	Low	Unclear	N/A	N/A	No/No/Yes PROBE design	Low	Unclear	Low	Unclear
Yasuhiko IINO (2003)[82]	Unclear	Unclear	N/A	Concomittant medications	No/No/No Open trial	High	Unclear	Unclear	Unclear
Black, H. R. (2001)[83]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Unclear/Unclear Double-blind, placebo-controlled	Unclear	high	Low	Unclear

Lubsen, J (2005)[84]	Unclear	Low	N/A	age, gender, race, concomittant medications, comorbidities	Yes/Unclear/Yes Double-blind, placebo-controlled (matching placebo)	Low	Low	Unclear	Unclear
Marin, R (2001)[85]	Unclear	Unclear	N/A	Race, concomittant medications	No/No/No	High	High	Low	Unclear
Chalmers, J (2000)[86]	Unclear	Unclear	Cross over: after an initial 12 weeks with active or placebo, non-responders were switched to take active treatment and were also changed to single blind (31.8% in placebo group)	Race, concomittant medications, comorbidities	Yes/Yes/Yes Double-blind, Placebo controlled	Low	Unclear	Unclear	Unclear
Otterstad, JE (1992)[87]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities, other	Yes/Yes/Unclear Identical tablets, add-on treatment open	Unclear	high	Unclear	Unclear
McMurray, JJ (2010)[88]	Low	Low	Comorbidities: metabolic syndrome at baseline valsartan vs. placebo (82.6% vs. 85.0%, p = 0.003)	N/A	Yes/Unclear/Yes Double-blind, placebo-controlled (matching placebo)	Low	Unclear	Unclear	High
Takahashi, A (2006)[89]	Low	Unclear	Concomittant medication: use of α-blockers at baseline in candesartan vs.control (21% vs. 3%, p=0.03)	Race	No/No/Yes PROBE	Low	Low	High	Unclear
Hou, FF. (2006)[90]	Low	Unclear	N/A	Comorbidities	Yes/Yes/Yes	Low	Low	Unclear	Unclear
Hoogerbrugge, N. (2002)[91]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	Yes/Unclear/Unclear Double-blind, placebo-controlled	Unclear	Unclear	Unclear	Unclear

Keane, WF, (1997)[92]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Unclear/Unclear/Unclear Double-blind, placebo-controlled	Unclear	Low	Unclear	Unclear
Materson, BJ (1993)[93]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Unclear Double-blind	Low	Unclear	Unclear	Unclear
Bremner, AD (1997)[94]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Unclear Double-blind, identical tablets	Low	Low	Unclear	Unclear
Puig JG (1991)[95]	Low	Unclear	N/A	Gender, race, concomittant medications, comorbidities	Yes/Yes/Unclear Double-blind	Low	Unclear	Unclear	Unclear
Komsuoglu, B (1989)[96]	Unclear	Unclear	N/A	Race, baseline BP, concomittant medications, comorbidities	No/No/No	High	high	Unclear	Unclear
Glaxo Group Research (1991)[97]	Unclear	Unclear	N/A	Race, concomittant medications, comorbidities	Yes/Unclear/Unclear	Low	Unclear	Unclear	Unclear
Ruggenenti, P (1999)[98]	Low	Low	N/A	Race, concomittant medications	Yes/Unclear/Unclear Double-blind, placebo-controlled	Low	Low	Unclear	Unclear
Yurenev, AP (1992)[99]	Low	Unclear	N/A	Gender, race, concomittant medications, comorbidities	Unclear/Unclear/Unclear	Unclear	Unclear	Unclear	Unclear
Talseth, T (1990)[100]	Low	Unclear	N/A	Age, gender, race, concomittant medications, comorbidities	No/No/No (for this portion of the trial); for first year Yes/Yes/Unclear - need to see initial publication	High	High	Unclear	Unclear
Zucchelli, P (1995)[101]	Unclear	Unclear	N/A	Race, concomittant	No/No/No	High	Low	Unclear	Unclear

				medications					
Yodfat, Y (1996)[102]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Unclear/Unclear Double-blind	Unclear	Unclear	Unclear	Unclear
MadGregor, MS (2005)[103]	Low	Low	Cross over: substantial crossover to a medication class of an alternative arm in patients who had trial drugs withdrawn (72%; 29% of all patients)	Race, concomittant medications, comorbidities	No/No/No	High	Unclear	Unclear	Unclear
Tepel, M (2007)[104]	Low	Low	N/A	Race, concomittant medications	Yes/Yes/Unclear	Low	Low	Unclear	Unclear
Bosch, J (2002)[105]	Unclear	Low	N/A	Age, gender, race, baseline BP, comorbidities	Yes/Unclear/Unclear Double-blind, placebo-controlled	Unclear	Low	Unclear	Unclear
Heesen, WF (2001)[106]	Unclear	Unclear	Comorbidities: patients with diabetes at baseline notably higher in the lisinopril vs. placebo group (8% vs. 2%)	Race, concomittant medications	Yes/Yes/Unclear Double-blind, Placebo controlled (identical tablets)	Low	Unclear	Unclear	Low
Terpstra, WF (2001)[107]	Unclear	Unclear	N/A	Gender, race, concomittant medications, comorbidities	Yes/Unclear/Unclear Double-blind	Unclear	Low	Unclear	Unclear
Ihle, BU. (-)[108]	Unclear	Unclear	Gender: more males in lisinopril vs. amlodipine group (64% vs. 38%)	Concomittant medications, comorbidities	Yes/Unclear/Unclear Double-blind, placebo controlled	Unclear	Unclear	Unclear	Unclear
Kamper, AL (1992)[109]	Low	Low	N/A	Race, concomittant medications,	No/No/No Unblinded	High	Unclear	Unclear	Low

				comorbidities					
Veterans Administration Cooperative Study on Antihypertensive Agents (1960)[110]	Unclear	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Unclear	Unclear	High	Unclear	Unclear
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1977)[111]	Unclear	Unclear	N/A	Race, comorbidities	Yes/Yes/Unclear Double-blind	Unclear	High	High	Unclear
Perez-Stable, EJ (1995)[112]	Low	Unclear	N/A	Concomittant medications, comorbidities	Yes/Yes/Unclear Placebo-controlled	Low	Unclear	Unclear	Low

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
MRC Working Party (1992)[25]	Moderate	Moderate	Moderate	Not reported	Not reported	Moderate	Moderate
Dahlof, B (1991)[26]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Low
SHEP Cooperative Research Group (1991)[27]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Perry, HM (1989)[28]	Moderate	Moderate	Not reported	Moderate	Moderate	Not reported	Moderate
Wikstrand, J (1988)[212]	Moderate	Moderate	Moderate	Not reported	High	Not reported	Low
Wilhelmsen, L (1987)[29]	Moderate	Moderate	Moderate	Not reported	High	Not reported	Moderate
Coope, J (1986)[30]	High	High	High	Not reported	High	Moderate	Moderate
Berglund, G (1986)[31]	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported	Moderate
The IPPPSH Collaborative Group (1985)[32]	Moderate	Moderate	Not reported	Moderate	Moderate	Moderate	Moderate
MRC working party (1985)[33]	Moderate	Moderate	Not reported	Moderate	Not reported	Moderate	Low
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982)[34]	Moderate	Moderate	Not reported	Moderate	Moderate	Moderate	Not reported
Sprackling, ME (1981)[35]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Helgeland, A (1980)[36]	Moderate	Moderate	Moderate	High	Not reported	Moderate	Moderate
The Australian Therapeutic Trial in Mild Hypertension	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
Committee (1980)[37]							
Perry, HM (1978)[38]	Moderate	Moderate	Not reported	Moderate	Not reported	Not reported	Moderate
The USPHS study- (1977)[39]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate
Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970)[40]	Moderate	Moderate	Not reported	Moderate	Moderate	Not reported	Moderate
Smith JM, (1967)[41]	Moderate	Moderate	Not reported	Not reported	High	Not reported	Moderate
Beckett, NS (2008)[42]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Low
Norris, K (2006)[43]	Not reported	Moderate	Moderate	Moderate	Not reported	Not reported	Moderate
Dahlöf, B (2005)[44]	Moderate	Moderate	Moderate	High	Not reported	Moderate	Low
Julius, S (2004)[45]	Moderate	Moderate	Moderate	Not reported	Not reported	Moderate	Low
Pepine, CJ (2003)[46]	Moderate	Moderate	Moderate	Not reported	Not reported	Moderate	Low
Bulpitt, CJ (2003)[48]	Not reported	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate
Malacco, E. (2003)[49]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate
Lithell, H (2003)[50]	Moderate	Moderate	Moderate	Not reported	Moderate	Not reported	Moderate
ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2002)[51]	Not reported	High	High	Not reported	Not reported	Not reported	Moderate

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
Zanchetti, A (2002)[52]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Low
Julius, S (2004)[53]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Brown, MJ (2000)[54]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Low
Hansson, L (2000)[55]	High	High	High	High	High	Not reported	Moderate
Hansson, L (1999)[56]	Moderate	Moderate	Moderate	Not reported	Not reported	Moderate	Moderate
National Intervention Cooperative Study in Elderly Hypertensives Study Group (1999)[57]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Borhani, NO (1996)[58]	Moderate	Moderate	Not reported	Not reported	Not reported	Moderate	Moderate
PATS Collaboration group (1995)[59]	Not reported	Moderate	Not reported	Not reported	Not reported	Not reported	Low
Gasiglia, E (1994)[60]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Amery, A (1985)[61]	Moderate	Moderate	Moderate	Not reported	Moderate	Moderate	Low
Rosei, EA (1997)[62]	Moderate	Moderate	Not reported	Moderate	Not reported	Not reported	Moderate
The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators (2008)[63]	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported	Not reported

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
Bakris, G. (2006)[64]	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported	Low
Zhang, Y (2011)[65]	Not reported	Moderate	Moderate	Not reported	Not reported	Moderate	Low
Zanchetti, A (2004)[66]	Moderate	Moderate	Not reported	Not reported	Not reported	Moderate	Moderate
Wing, LMH (2003)[67]	Moderate	Moderate	Moderate	Not reported	Not reported	Not reported	Low
PROGRESS Collaborative Group (2001)[68]	Not reported	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported
Staessen, JA (2000)[69]	Moderate	Moderate	Not reported	Not reported	Moderate	Moderate	Low
Maschio, G (1996)[70]	Moderate	Moderate	Not reported	Not reported	Not reported	Moderate	Moderate
Lindholm, LH (2003)[71]	Moderate	Moderate	Moderate	Moderate	Not reported	Moderate	Not reported
The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) (1997)[72]	Moderate	Not reported	Not reported	Not reported	Not reported	high	Moderate
Kumagai, H (2000)[73]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Tedesco, MA (1999)[74]	Not reported	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported
Perez-Stable, EJ (2000)[75]	Not reported	Not reported	Not reported	Moderate	Moderate	Not reported	Not reported
Neutel, JM (1999)[76]	Not reported	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported
Schmieder, RE (2009)[77]	High	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Stanton, AV. (2001)[78]	Not reported	Moderate	Not reported	Moderate	Not reported	Moderate	Not reported

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
T Hannedouche (1994)[79]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Yoshiki YUI (2003)[80]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate
Narumi, H (2011)[81]	Moderate	Moderate	Moderate	Not reported	Not reported	Not reported	Low
Yasuhiko IINO (2003)[82]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Black, H. R. (2001)[83]	Not reported	Not reported	Not reported	Not reported	Moderate	Not reported	Moderate
Lubsen, J (2005)[84]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Low
Marin, R (2001)[85]	High	High	Not reported	Not reported	Not reported	High	Moderate
Chalmers, J (2000)[86]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Otterstad, JE (1992)[87]	Moderate	Not reported	Not reported	Moderate	Not reported	Moderate	Not reported
McMurray, JJ (2010)[88]	High	High	High	Not reported	Not reported	Not reported	Moderate
Takahashi, A (2006)[89]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Hou, FF. (2006)[90]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Low
Hoogerbrugge, N. (2002)[91]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported
Keane, WF, (1997)[92]	Moderate	Moderate	Not reported	Moderate	Not reported	Not reported	Moderate
Materson, BJ (1993)[93]	Not reported	Not reported	Not reported	Moderate	Not reported	Not reported	Not reported
Bremner, AD (1997)[94]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Low
Puig JG (1991)[95]	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

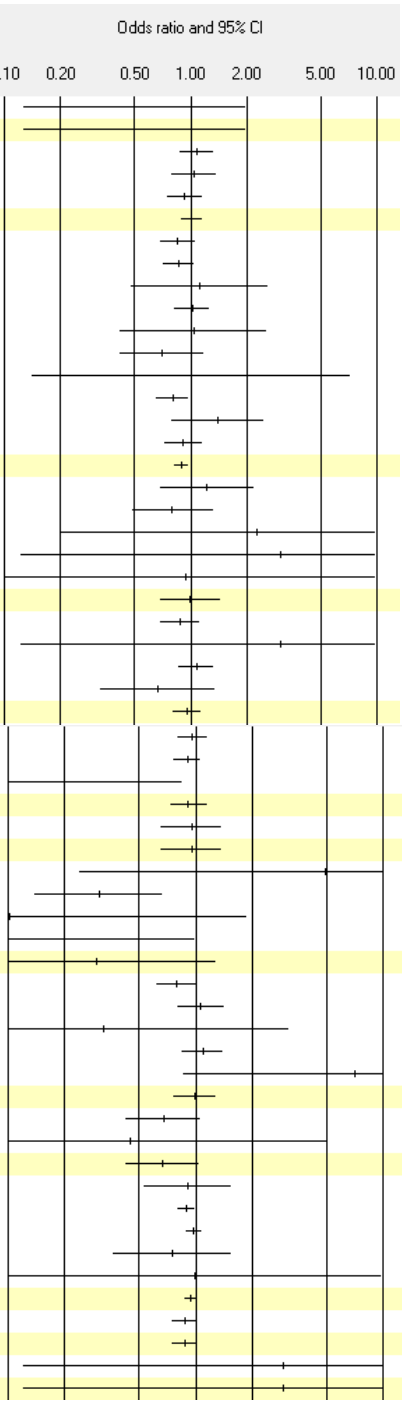
Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
Komsuoglu, B (1989)[96]	Not reported	Not reported	Not reported	High	Not reported	High	Moderate
Glaxo Group Research (1991)[97]	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported	Low
Ruggenenti, P (1999)[98]	Not reported	Moderate	Not reported	Not reported	Not reported	Moderate	Moderate
Yurenev, AP (1992)[99]	Moderate	Moderate	Not reported	Not reported	Not reported	Not reported	Moderate
Talseth, T (1990)[100]	High	Not reported	Not reported	Not reported	Not reported	Not reported	High
Zucchelli, P (1995)[101]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Yodfat, Y (1996)[102]	Not reported	Not reported	Not reported	Moderate	Moderate	Not reported	Not reported
MadGregor, MS (2005)[103]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	High
Tepel, M (2007)[104]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Low
Bosch, J (2002)[105]	Moderate	Not reported	Moderate	Not reported	Not reported	Not reported	Not reported
Heesen, WF (2001)[106]	Moderate	Moderate	Not reported	Not reported	Not reported	Moderate	Moderate
Terpstra, WF (2001)[107]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Low
Ihle, BU. (-)[108]	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Kamper, AL (1992)[109]	Moderate	Not reported	Not reported	Not reported	Not reported	Not reported	Moderate
Veterans Administration Cooperative Study on Antihypertensive Agents (1960)[110]	Not reported	Not reported	Not reported	High	High	Not reported	Moderate
Veterans Administration Cooperative Study Group on	Moderate	Moderate	Moderate	Moderate	Moderate	Not reported	Moderate

Study-specific outcome level assessments: High, Moderate, Low or Not reported							
Study	**Myocardial Infarction**	**Stroke**	**Diabetes**	**Sexual dysfunction**	**Depression**	**Cancer**	**Mortality (all cause and/or CV mortality)**
Antihypertensive Agents (1977)[111]							
Perez-Stable, EJ (1995)[112]	Not reported	Not reported	Not reported	Moderate	Moderate	Not reported	Not reported

Appendix 3:
Summary of Pairwise Meta-Analyses

Overall Mortality

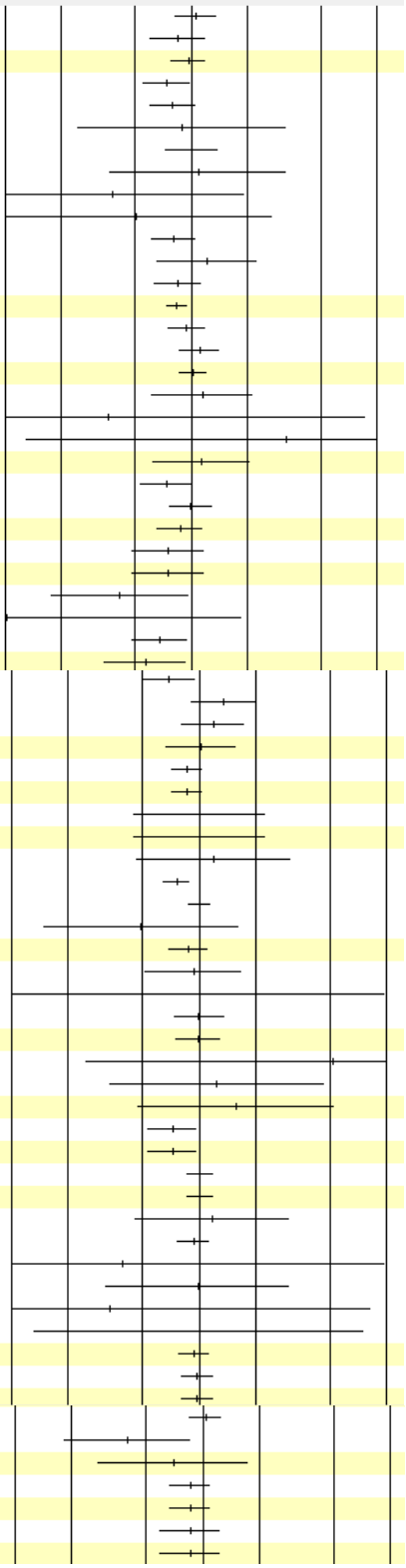
Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	110.00	22044.000	110.000	0.496	0.126	1.956	-1.002	0.316
Random	110.00			0.496	0.126	1.956	-1.002	0.316
	12.00	10042.000	12.000	1.076	0.878	1.319	0.708	0.479
	12.00	10128.000	12.000	1.035	0.787	1.362	0.249	0.803
	12.00	10129.000	12.000	0.930	0.746	1.160	-0.642	0.521
Random	12.00			1.013	0.889	1.155	0.194	0.846
	13.00	10042.000	13.000	0.853	0.687	1.059	-1.443	0.149
	13.00	10053.000	13.000	0.871	0.717	1.057	-1.401	0.161
	13.00	10087.000	13.000	1.123	0.482	2.619	0.269	0.788
	13.00	10129.000	13.000	1.020	0.822	1.265	0.175	0.861
	13.00	10157.000	13.000	1.038	0.417	2.583	0.081	0.936
	13.00	10159.000	13.000	0.704	0.419	1.181	-1.330	0.183
	13.00	10165.000	13.000	1.016	0.142	7.284	0.016	0.988
	13.00	10179.000	13.000	0.805	0.659	0.985	-2.111	0.035
	13.00	10199.000	13.000	1.391	0.789	2.453	1.141	0.254
	13.00	10328.000	13.000	0.914	0.725	1.152	-0.761	0.447
Random	13.00			0.894	0.816	0.978	-2.440	0.015
	14.00	10199.000	14.000	1.227	0.687	2.191	0.693	0.489
	14.00	10542.000	14.000	0.797	0.485	1.311	-0.894	0.371
	14.00	10545.000	14.000	2.289	0.204	25.750	0.671	0.502
	14.00	11483.000	14.000	3.056	0.123	75.866	0.682	0.495
	14.00	12558.000	14.000	0.943	0.057	15.697	-0.041	0.967
Random	14.00			0.991	0.686	1.431	-0.047	0.963
	15.00	10529.000	15.000	0.873	0.686	1.110	-1.109	0.267
	15.00	11315.000	15.000	3.071	0.123	76.449	0.684	0.494
	15.00	11411.000	15.000	1.078	0.869	1.337	0.685	0.493
	15.00	12103.000	15.000	0.669	0.329	1.360	-1.111	0.267
Random	15.00			0.962	0.812	1.140	-0.448	0.654
	16.00	10203.000	16.000	0.963	0.804	1.154	-0.407	0.684
	16.00	11464.000	16.000	0.905	0.769	1.065	-1.206	0.228
	16.00	11482.000	16.000	0.047	0.003	0.849	-2.070	0.038
Random	16.00			0.917	0.735	1.143	-0.772	0.440
	17.00	10111.000	17.000	0.959	0.660	1.395	-0.218	0.827
Random	17.00			0.959	0.660	1.395	-0.218	0.827
	18.00	10162.000	18.000	4.980	0.239	103.995	1.035	0.300
	18.00	10170.000	18.000	0.306	0.139	0.673	-2.943	0.003
	18.00	10172.000	18.000	0.101	0.005	1.903	-1.531	0.126
	18.00	11434.000	18.000	0.047	0.002	0.991	-1.966	0.049
Random	18.00			0.294	0.067	1.286	-1.626	0.104
	23.00	10042.000	23.000	0.792	0.620	1.012	-1.866	0.062
	23.00	10100.000	23.000	1.062	0.800	1.410	0.416	0.677
	23.00	10123.000	23.000	0.321	0.032	3.185	-0.971	0.331
	23.00	10129.000	23.000	1.096	0.851	1.411	0.710	0.478
	23.00	11653.000	23.000	7.095	0.862	58.385	1.822	0.068
Random	23.00			0.985	0.760	1.277	-0.115	0.909
	24.00	10185.000	24.000	0.677	0.428	1.071	-1.668	0.095
	24.00	11174.000	24.000	0.451	0.040	5.140	-0.641	0.521
Random	24.00			0.667	0.425	1.048	-1.758	0.079
	25.00	10185.000	25.000	0.903	0.530	1.536	-0.378	0.705
	25.00	10187.000	25.000	0.890	0.802	0.987	-2.211	0.027
	25.00	10198.000	25.000	0.980	0.889	1.080	-0.414	0.679
	25.00	10213.000	25.000	0.749	0.362	1.549	-0.780	0.436
	25.00	11628.000	25.000	0.989	0.062	15.891	-0.008	0.994
Random	25.00			0.934	0.871	1.002	-1.914	0.056
	26.00	10221.000	26.000	0.875	0.758	1.011	-1.816	0.069
Random	26.00			0.875	0.758	1.011	-1.816	0.069
	310.00	11137.000	310.000	2.952	0.120	72.627	0.663	0.508
Random	310.00			2.952	0.120	72.627	0.663	0.508



Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study					Odds ratio and 95% CI
				Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.10 0.20 0.50 1.00 2.00 5.00 10.00
	34.00	10199.000	34.000	0.882	0.515	1.511	-0.457	0.648	
	34.00	10210.000	34.000	1.064	0.958	1.182	1.158	0.247	
	34.00	10523.000	34.000	0.913	0.747	1.116	-0.887	0.375	
Random	34.00			1.023	0.929	1.125	0.456	0.648	
	35.00	10201.000	35.000	1.220	0.941	1.582	1.499	0.134	
	35.00	10210.000	35.000	0.970	0.871	1.080	-0.554	0.580	
	35.00	10309.000	35.000	0.885	0.338	2.315	-0.249	0.803	
	35.00	10388.000	35.000	1.252	0.335	4.681	0.334	0.739	
Random	35.00			1.003	0.909	1.107	0.060	0.952	
	38.00	10512.000	38.000	0.740	0.578	0.948	-2.381	0.017	
Random	38.00			0.740	0.578	0.948	-2.381	0.017	
	45.00	10185.000	45.000	1.334	0.760	2.342	1.003	0.316	
	45.00	10210.000	45.000	0.912	0.810	1.027	-1.522	0.128	
	45.00	10249.000	45.000	0.948	0.810	1.110	-0.664	0.507	
	45.00	11034.000	45.000	0.393	0.015	10.121	-0.564	0.573	
	45.00	11222.000	45.000	0.791	0.368	1.701	-0.600	0.549	
	45.00	11425.000	45.000	1.769	0.486	6.435	0.866	0.387	
	45.00	11718.000	45.000	0.333	0.013	8.346	-0.669	0.504	
	45.00	12014.000	45.000	0.720	0.146	3.560	-0.403	0.687	
	45.00	12538.000	45.000	3.186	0.128	79.354	0.706	0.480	
Random	45.00			0.934	0.851	1.024	-1.456	0.145	
	46.00	11546.000	46.000	0.497	0.069	3.560	-0.696	0.486	
Random	46.00			0.497	0.069	3.560	-0.696	0.486	
	47.00	10249.000	47.000	0.961	0.821	1.125	-0.495	0.620	
Random	47.00			0.961	0.821	1.125	-0.495	0.620	
	510.00	10355.000	510.000	0.927	0.465	1.848	-0.216	0.829	
Random	510.00			0.927	0.465	1.848	-0.216	0.829	
	56.00	10193.000	56.000	1.024	0.924	1.133	0.448	0.654	
	56.00	11279.000	56.000	0.667	0.111	4.007	-0.443	0.658	
	56.00	11304.000	56.000	1.017	0.020	52.115	0.008	0.993	
Random	56.00			1.022	0.923	1.132	0.422	0.673	
	57.00	10249.000	57.000	1.014	0.865	1.188	0.169	0.866	
	57.00	10355.000	57.000	0.540	0.303	0.964	-2.084	0.037	
Random	57.00			0.789	0.431	1.443	-0.769	0.442	
	58.00	10236.000	58.000	0.991	0.787	1.247	-0.079	0.937	
Random	58.00			0.991	0.787	1.247	-0.079	0.937	
	59.00	10237.000	59.000	0.975	0.809	1.175	-0.266	0.790	
Random	59.00			0.975	0.809	1.175	-0.266	0.790	
	710.00	10355.000	710.000	1.716	0.824	3.573	1.442	0.149	
Random	710.00			1.716	0.824	3.573	1.442	0.149	

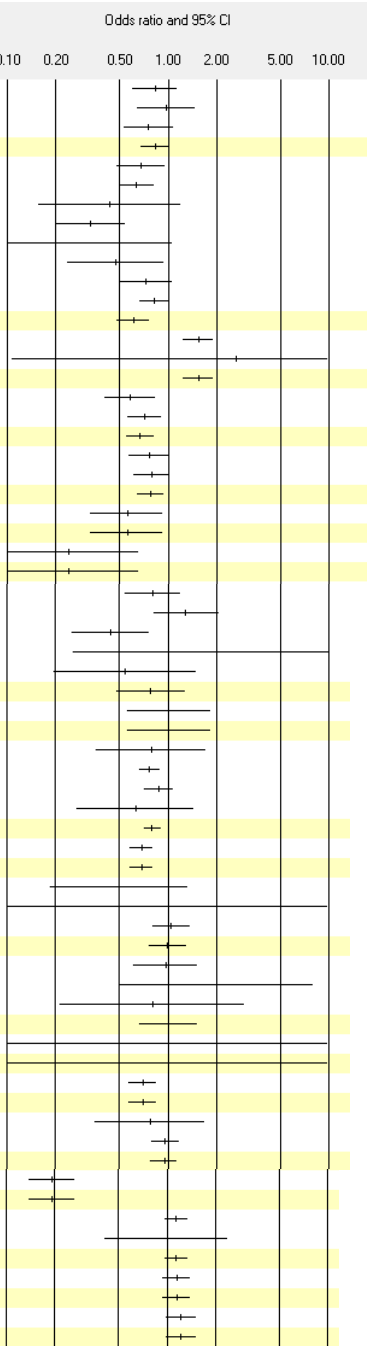
Cardiovascular Mortality

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	12.00	10042.000	12.000	1.066	0.822	1.382	0.479	0.632
	12.00	10129.000	12.000	0.845	0.601	1.190	-0.962	0.336
Random	12.00			0.976	0.783	1.216	-0.217	0.828
	13.00	10042.000	13.000	0.734	0.548	0.983	-2.072	0.038
	13.00	10053.000	13.000	0.798	0.601	1.059	-1.561	0.119
	13.00	10087.000	13.000	0.891	0.244	3.251	-0.174	0.862
	13.00	10129.000	13.000	1.011	0.731	1.399	0.067	0.946
	13.00	10157.000	13.000	1.091	0.363	3.275	0.155	0.877
	13.00	10159.000	13.000	0.377	0.072	1.970	-1.156	0.248
	13.00	10165.000	13.000	0.503	0.091	2.777	-0.789	0.430
	13.00	10179.000	13.000	0.799	0.608	1.050	-1.608	0.108
	13.00	10199.000	13.000	1.223	0.656	2.280	0.632	0.527
	13.00	10328.000	13.000	0.852	0.636	1.140	-1.079	0.280
Random	13.00			0.837	0.738	0.949	-2.776	0.006
	14.00	10203.000	14.000	0.944	0.747	1.194	-0.480	0.631
	14.00	11464.000	14.000	1.117	0.866	1.441	0.853	0.394
Random	14.00			1.020	0.858	1.212	0.225	0.822
	15.00	10199.000	15.000	1.152	0.614	2.161	0.442	0.659
	15.00	11510.000	15.000	0.355	0.014	8.782	-0.633	0.527
	15.00	12558.000	15.000	3.269	0.129	83.026	0.718	0.473
Random	15.00			1.146	0.625	2.101	0.441	0.660
	16.00	10529.000	16.000	0.741	0.531	1.032	-1.772	0.076
	16.00	11411.000	16.000	0.996	0.761	1.302	-0.032	0.975
Random	16.00			0.873	0.655	1.165	-0.922	0.357
	17.00	10111.000	17.000	0.757	0.481	1.191	-1.205	0.228
Random	17.00			0.757	0.481	1.191	-1.205	0.228
	19.00	10170.000	19.000	0.414	0.177	0.970	-2.029	0.042
	19.00	10172.000	19.000	0.101	0.005	1.903	-1.531	0.126
	19.00	10380.000	19.000	0.683	0.482	0.968	-2.144	0.032
Random	19.00			0.565	0.340	0.941	-2.195	0.028
	23.00	10042.000	23.000	0.689	0.498	0.955	-2.238	0.025
	23.00	10100.000	23.000	1.356	0.905	2.033	1.476	0.140
	23.00	10129.000	23.000	1.196	0.810	1.767	0.900	0.368
Random	23.00			1.024	0.667	1.573	0.108	0.914
	24.00	10221.000	24.000	0.862	0.712	1.045	-1.507	0.132
Random	24.00			0.862	0.712	1.045	-1.507	0.132
	25.00	10185.000	25.000	1.012	0.450	2.277	0.028	0.977
Random	25.00			1.012	0.450	2.277	0.028	0.977
	26.00	10185.000	26.000	1.192	0.462	3.071	0.363	0.717
	26.00	10187.000	26.000	0.761	0.646	0.896	-3.281	0.001
	26.00	10198.000	26.000	1.004	0.876	1.150	0.056	0.956
	26.00	10213.000	26.000	0.490	0.147	1.631	-1.163	0.245
Random	26.00			0.874	0.689	1.110	-1.103	0.270
	35.00	10199.000	35.000	0.942	0.517	1.718	-0.193	0.847
	35.00	10519.000	35.000	1.000	0.020	50.785	0.000	1.000
	35.00	10523.000	35.000	0.998	0.733	1.359	-0.011	0.991
Random	35.00			0.986	0.750	1.297	-0.098	0.922
	36.00	10251.000	36.000	5.198	0.248	108.926	1.062	0.288
	36.00	10388.000	36.000	1.252	0.335	4.681	0.334	0.739
Random	36.00			1.568	0.468	5.259	0.728	0.466
	39.00	10512.000	39.000	0.723	0.534	0.980	-2.093	0.036
Random	39.00			0.723	0.534	0.980	-2.093	0.036
	46.00	10193.000	46.000	1.007	0.856	1.185	0.087	0.930
Random	46.00			1.007	0.856	1.185	0.087	0.930
	56.00	10185.000	56.000	1.178	0.457	3.035	0.339	0.735
	56.00	10249.000	56.000	0.936	0.768	1.140	-0.660	0.509
	56.00	11034.000	56.000	0.393	0.015	10.121	-0.564	0.573
	56.00	11222.000	56.000	0.993	0.319	3.091	-0.013	0.990
	56.00	11718.000	56.000	0.333	0.013	8.346	-0.669	0.504
	56.00	12014.000	56.000	1.000	0.131	7.644	0.000	1.000
Random	56.00			0.940	0.778	1.136	-0.638	0.523
	57.00	10249.000	57.000	0.971	0.799	1.181	-0.290	0.772
Random	57.00			0.971	0.799	1.181	-0.290	0.772
	67.00	10249.000	67.000	1.038	0.851	1.266	0.371	0.711
	67.00	10355.000	67.000	0.399	0.183	0.872	-2.303	0.021
Random	67.00			0.696	0.276	1.754	-0.769	0.442
	68.00	10237.000	68.000	0.865	0.672	1.115	-1.120	0.263
Random	68.00			0.865	0.672	1.115	-1.120	0.263
	69.00	10236.000	69.000	0.862	0.593	1.254	-0.774	0.439
Random	69.00			0.862	0.593	1.254	-0.774	0.439



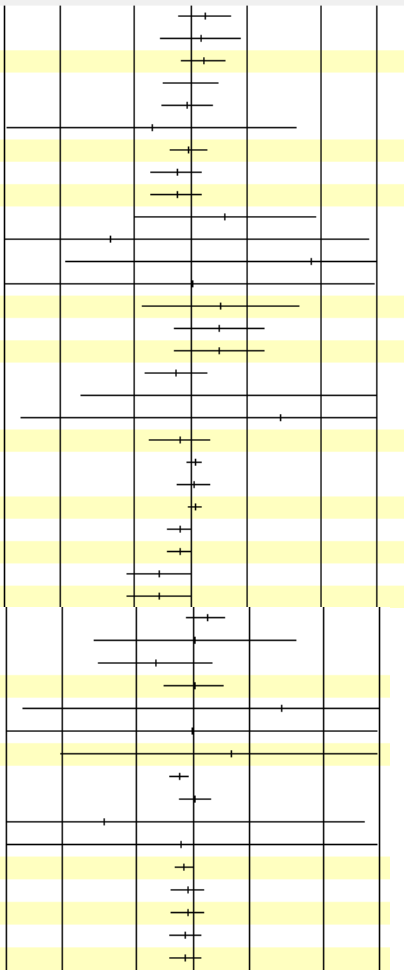
Stroke

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Group-A	Group-B
	12.00	10042.000	12.000	0.831	0.603	1.145	-1.134	0.257	56 / 1102	134 / 2213
	12.00	10128.000	12.000	0.974	0.644	1.473	-0.125	0.900	45 / 3185	46 / 3172
	12.00	10129.000	12.000	0.755	0.528	1.080	-1.539	0.124	42 / 4403	109 / 8654
Random	12.00			0.837	0.681	1.030	-1.684	0.092		
	13.00	10042.000	13.000	0.674	0.477	0.952	-2.237	0.025	45 / 1081	134 / 2213
	13.00	10053.000	13.000	0.636	0.494	0.817	-3.532	0.000	106 / 2365	163 / 2371
	13.00	10087.000	13.000	0.433	0.156	1.198	-1.612	0.107	11 / 443	6 / 108
	13.00	10129.000	13.000	0.330	0.200	0.544	-4.349	0.000	18 / 4297	109 / 8654
	13.00	10157.000	13.000	0.061	0.003	1.070	-1.913	0.056	1 / 407	8 / 379
	13.00	10159.000	13.000	0.472	0.236	0.943	-2.127	0.033	12 / 1721	25 / 1706
	13.00	10179.000	13.000	0.724	0.501	1.045	-1.723	0.085	51 / 1933	69 / 1912
	13.00	10328.000	13.000	0.823	0.665	1.017	-1.804	0.071	159 / 2481	217 / 2824
Random	13.00			0.608	0.483	0.765	-4.247	0.000		
	14.00	10525.000	14.000	1.541	1.244	1.910	3.952	0.000	235 / 1452	163 / 1464
	14.00	11647.000	14.000	2.665	0.107	66.269	0.598	0.550	2 / 100	1 / 88
Random	14.00			1.545	1.247	1.914	3.983	0.000		
	15.00	10529.000	15.000	0.578	0.403	0.829	-2.982	0.003	49 / 2398	80 / 2297
	15.00	11411.000	15.000	0.711	0.559	0.905	-2.777	0.005	123 / 1975	171 / 2002
Random	15.00			0.667	0.546	0.815	-3.966	0.000		
	16.00	10203.000	16.000	0.760	0.573	1.008	-1.904	0.057	89 / 2477	115 / 2460
	16.00	11464.000	16.000	0.798	0.616	1.035	-1.700	0.089	105 / 4631	132 / 4675
Random	16.00			0.781	0.645	0.945	-2.540	0.011		
	17.00	10111.000	17.000	0.556	0.330	0.937	-2.203	0.028	23 / 419	44 / 465
Random	17.00			0.556	0.330	0.937	-2.203	0.028		
	18.00	10170.000	18.000	0.240	0.088	0.654	-2.789	0.005	5 / 186	20 / 194
Random	18.00			0.240	0.088	0.654	-2.789	0.005		
	23.00	10042.000	23.000	0.811	0.543	1.212	-1.020	0.308	45 / 1081	56 / 1102
	23.00	10100.000	23.000	1.295	0.813	2.061	1.089	0.276	41 / 3272	32 / 3297
	23.00	10129.000	23.000	0.437	0.251	0.760	-2.932	0.003	18 / 4297	42 / 4403
	23.00	10145.000	23.000	5.034	0.258	98.332	1.066	0.286	4 / 178	1 / 126
	23.00	11653.000	23.000	0.542	0.195	1.504	-1.177	0.239	6 / 150	11 / 154
Random	23.00			0.782	0.478	1.277	-0.984	0.325		
	24.00	10185.000	24.000	1.012	0.559	1.833	0.040	0.968	23 / 436	23 / 441
Random	24.00			1.012	0.559	1.833	0.040	0.968		
	25.00	10185.000	25.000	0.786	0.357	1.730	-0.597	0.550	9 / 217	23 / 441
	25.00	10187.000	25.000	0.765	0.660	0.887	-3.562	0.000	327 / 9639	422 / 9618
	25.00	10198.000	25.000	0.877	0.715	1.075	-1.261	0.207	176 /	201 /
	25.00	10213.000	25.000	0.629	0.271	1.459	-1.080	0.280	9 / 1177	14 / 1157
Random	25.00			0.798	0.710	0.897	-3.789	0.000		
	26.00	10221.000	26.000	0.691	0.585	0.815	-4.372	0.000	255 / 4605	359 / 4588
Random	26.00			0.691	0.585	0.815	-4.372	0.000		
	34.00	10199.000	34.000	0.499	0.185	1.341	-1.378	0.168	6 / 426	12 / 431
	34.00	10519.000	34.000	1.000	0.020	50.785	0.000	1.000	1 / 128	1 / 128
	34.00	10523.000	34.000	1.047	0.799	1.371	0.332	0.740	112 / 3044	107 / 3039
Random	34.00			0.992	0.761	1.294	-0.057	0.954		
	35.00	10201.000	35.000	0.970	0.611	1.540	-0.127	0.899	37 / 942	38 / 940
	35.00	10309.000	35.000	2.009	0.499	8.085	0.982	0.326	6 / 442	3 / 441
	35.00	10388.000	35.000	0.799	0.214	2.987	-0.334	0.739	4 / 707	5 / 707
Random	35.00			1.016	0.670	1.540	0.074	0.941		
	36.00	10543.000	36.000	1.000	0.020	50.649	0.000	1.000	1 / 197	1 / 197
Random	36.00			1.000	0.020	50.649	0.000	1.000		
	38.00	10512.000	38.000	0.698	0.574	0.850	-3.578	0.000	177 / 4841	251 / 4870
Random	38.00			0.698	0.574	0.850	-3.578	0.000		
	45.00	10185.000	45.000	0.777	0.353	1.709	-0.627	0.530	9 / 217	23 / 436
	45.00	10249.000	45.000	0.963	0.788	1.177	-0.365	0.715	207 / 2196	215 / 2205
Random	45.00			0.951	0.783	1.155	-0.509	0.611		
	47.00	10249.000	47.000	0.192	0.139	0.266	-9.887	0.000	45 / 2213	215 / 2205
Random	47.00			0.192	0.139	0.266	-9.887	0.000		
	56.00	10193.000	56.000	1.144	0.972	1.347	1.616	0.106	322 / 7649	281 / 7596
	56.00	11279.000	56.000	1.002	0.413	2.428	0.004	0.996	10 / 510	10 / 511
Random	56.00			1.139	0.970	1.337	1.590	0.112		
	57.00	10249.000	57.000	1.152	0.947	1.403	1.415	0.157	237 / 2213	207 / 2196
Random	57.00			1.152	0.947	1.403	1.415	0.157		
	59.00	10237.000	59.000	1.227	0.992	1.518	1.886	0.059	196 / 5471	159 / 5410
Random	59.00			1.227	0.992	1.518	1.886	0.059		



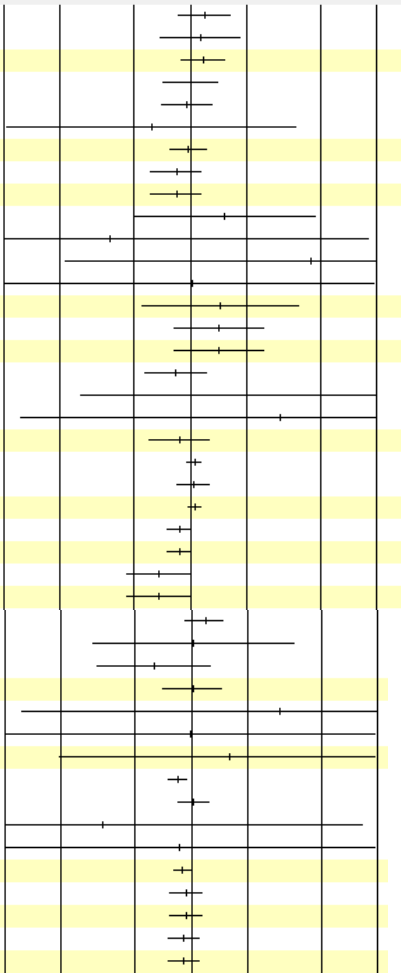
Myocardial Infarction

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	12.00	10042.000	12.000	1.208	0.868	1.681	1.119	0.263
	12.00	10128.000	12.000	1.135	0.687	1.873	0.494	0.621
Random	12.00			1.185	0.899	1.562	1.206	0.228
	13.00	10042.000	13.000	1.014	0.714	1.439	0.077	0.939
	13.00	10053.000	13.000	0.963	0.698	1.329	-0.231	0.818
	13.00	10157.000	13.000	0.620	0.103	3.734	-0.521	0.602
Random	13.00			0.978	0.773	1.237	-0.185	0.853
	14.00	10529.000	14.000	0.848	0.615	1.169	-1.007	0.314
Random	14.00			0.848	0.615	1.169	-1.007	0.314
	15.00	10542.000	15.000	1.523	0.492	4.713	0.730	0.465
	15.00	10545.000	15.000	0.372	0.015	9.254	-0.604	0.546
	15.00	11647.000	15.000	4.487	0.212	94.753	0.965	0.335
	15.00	12537.000	15.000	1.021	0.020	52.472	0.010	0.992
Random	15.00			1.458	0.550	3.864	0.758	0.448
	16.00	10111.000	16.000	1.429	0.813	2.512	1.241	0.215
Random	16.00			1.429	0.813	2.512	1.241	0.215
	23.00	10042.000	23.000	0.839	0.569	1.238	-0.884	0.377
	23.00	10145.000	23.000	5.034	0.258	98.332	1.066	0.286
	23.00	11447.000	23.000	3.061	0.122	76.949	0.680	0.497
Random	23.00			0.881	0.601	1.291	-0.652	0.514
	24.00	10187.000	24.000	1.061	0.964	1.167	1.213	0.225
	24.00	10198.000	24.000	1.037	0.846	1.271	0.348	0.728
Random	24.00			1.056	0.969	1.151	1.246	0.213
	25.00	10221.000	25.000	0.880	0.752	1.030	-1.593	0.111
Random	25.00			0.880	0.752	1.030	-1.593	0.111
	33.00	10512.000	33.000	0.679	0.458	1.006	-1.929	0.054
Random	33.00			0.679	0.458	1.006	-1.929	0.054
	34.00	10236.000	34.000	1.190	0.931	1.521	1.390	0.164
	34.00	10251.000	34.000	1.030	0.294	3.613	0.046	0.963
	34.00	10309.000	34.000	0.638	0.313	1.299	-1.239	0.215
Random	34.00			1.027	0.705	1.494	0.138	0.891
	35.00	10519.000	35.000	3.024	0.122	74.928	0.676	0.499
	35.00	10543.000	35.000	0.995	0.062	16.019	-0.004	0.997
Random	35.00			1.602	0.196	13.093	0.439	0.660
	45.00	10193.000	45.000	0.847	0.749	0.958	-2.652	0.008
	45.00	10249.000	45.000	1.032	0.845	1.261	0.313	0.754
	45.00	11156.000	45.000	0.333	0.013	8.471	-0.666	0.506
	45.00	11425.000	45.000	0.867	0.054	14.026	-0.100	0.920
Random	45.00			0.896	0.802	1.002	-1.917	0.055
	46.00	10249.000	46.000	0.945	0.771	1.158	-0.549	0.583
Random	46.00			0.945	0.771	1.158	-0.549	0.583
	56.00	10249.000	56.000	0.915	0.747	1.120	-0.863	0.388
Random	56.00			0.915	0.747	1.120	-0.863	0.388



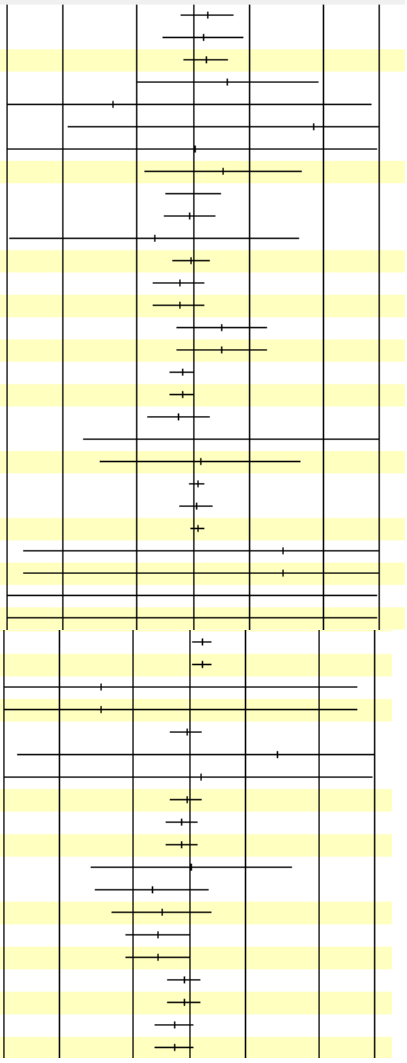
Incident Diabetes

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	12.00	10042.000	12.000	1.208	0.868	1.681	1.119	0.263
	12.00	10128.000	12.000	1.135	0.687	1.873	0.494	0.621
Random	12.00			1.185	0.899	1.562	1.206	0.228
	13.00	10042.000	13.000	1.014	0.714	1.439	0.077	0.939
	13.00	10053.000	13.000	0.963	0.698	1.329	-0.231	0.818
	13.00	10157.000	13.000	0.620	0.103	3.734	-0.521	0.602
Random	13.00			0.978	0.773	1.237	-0.185	0.853
	14.00	10529.000	14.000	0.848	0.615	1.169	-1.007	0.314
Random	14.00			0.848	0.615	1.169	-1.007	0.314
	15.00	10542.000	15.000	1.523	0.492	4.713	0.730	0.465
	15.00	10545.000	15.000	0.372	0.015	9.254	-0.604	0.546
	15.00	11647.000	15.000	4.487	0.212	94.753	0.965	0.335
	15.00	12537.000	15.000	1.021	0.020	52.472	0.010	0.992
Random	15.00			1.458	0.550	3.864	0.758	0.448
	16.00	10111.000	16.000	1.429	0.813	2.512	1.241	0.215
Random	16.00			1.429	0.813	2.512	1.241	0.215
	23.00	10042.000	23.000	0.839	0.569	1.238	-0.884	0.377
	23.00	10145.000	23.000	5.034	0.258	98.332	1.066	0.286
	23.00	11447.000	23.000	3.061	0.122	76.949	0.680	0.497
Random	23.00			0.881	0.601	1.291	-0.652	0.514
	24.00	10187.000	24.000	1.061	0.964	1.167	1.213	0.225
	24.00	10198.000	24.000	1.037	0.846	1.271	0.348	0.728
Random	24.00			1.056	0.969	1.151	1.246	0.213
	25.00	10221.000	25.000	0.880	0.752	1.030	-1.593	0.111
Random	25.00			0.880	0.752	1.030	-1.593	0.111
	33.00	10512.000	33.000	0.679	0.458	1.006	-1.929	0.054
Random	33.00			0.679	0.458	1.006	-1.929	0.054
	34.00	10236.000	34.000	1.190	0.931	1.521	1.390	0.164
	34.00	10251.000	34.000	1.030	0.294	3.613	0.046	0.963
	34.00	10309.000	34.000	0.638	0.313	1.299	-1.239	0.215
Random	34.00			1.027	0.705	1.494	0.138	0.891
	35.00	10519.000	35.000	3.024	0.122	74.928	0.676	0.499
	35.00	10543.000	35.000	0.995	0.062	16.019	-0.004	0.997
Random	35.00			1.602	0.196	13.093	0.439	0.660
	45.00	10193.000	45.000	0.847	0.749	0.958	-2.652	0.008
	45.00	10249.000	45.000	1.032	0.845	1.261	0.313	0.754
	45.00	11156.000	45.000	0.333	0.013	8.471	-0.666	0.506
	45.00	11425.000	45.000	0.867	0.054	14.026	-0.100	0.920
Random	45.00			0.896	0.802	1.002	-1.917	0.055
	46.00	10249.000	46.000	0.945	0.771	1.158	-0.549	0.583
Random	46.00			0.945	0.771	1.158	-0.549	0.583
	56.00	10249.000	56.000	0.915	0.747	1.120	-0.863	0.388
Random	56.00			0.915	0.747	1.120	-0.863	0.388



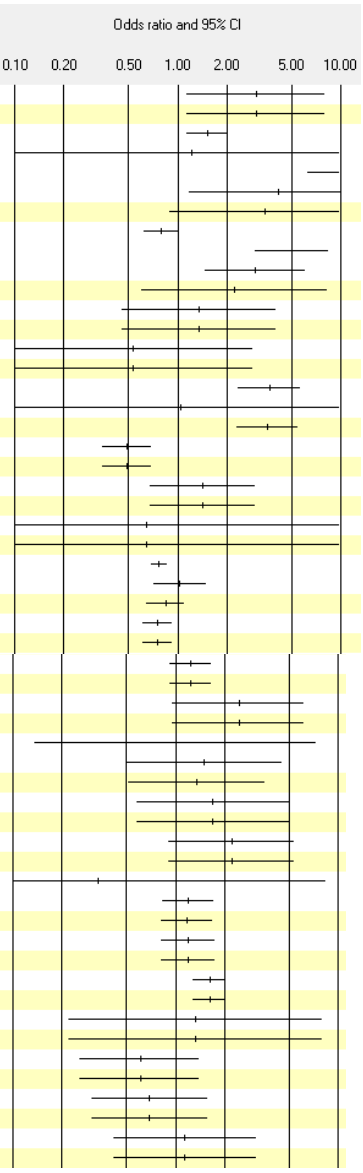
Cancers

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	12.00	10042.000	12.000	1.208	0.868	1.681	1.119	0.263
	12.00	10128.000	12.000	1.135	0.687	1.873	0.494	0.621
Random	12.00			1.185	0.899	1.562	1.206	0.228
	14.00	10542.000	14.000	1.523	0.492	4.713	0.730	0.465
	14.00	10545.000	14.000	0.372	0.015	9.254	-0.604	0.546
	14.00	11647.000	14.000	4.487	0.212	94.753	0.965	0.335
	14.00	12537.000	14.000	1.021	0.020	52.472	0.010	0.992
Random	14.00			1.458	0.550	3.864	0.758	0.448
	15.00	10042.000	15.000	1.014	0.714	1.439	0.077	0.939
	15.00	10053.000	15.000	0.963	0.698	1.329	-0.231	0.818
	15.00	10157.000	15.000	0.620	0.103	3.734	-0.521	0.602
Random	15.00			0.978	0.773	1.237	-0.185	0.853
	16.00	10529.000	16.000	0.848	0.615	1.169	-1.007	0.314
Random	16.00			0.848	0.615	1.169	-1.007	0.314
	17.00	10111.000	17.000	1.429	0.813	2.512	1.241	0.215
Random	17.00			1.429	0.813	2.512	1.241	0.215
	23.00	10221.000	23.000	0.880	0.752	1.030	-1.593	0.111
Random	23.00			0.880	0.752	1.030	-1.593	0.111
	25.00	10042.000	25.000	0.839	0.569	1.238	-0.884	0.377
	25.00	10145.000	25.000	5.034	0.258	98.332	1.066	0.286
Random	25.00			1.094	0.315	3.804	0.141	0.888
	26.00	10187.000	26.000	1.061	0.964	1.167	1.213	0.225
	26.00	10198.000	26.000	1.037	0.846	1.271	0.348	0.728
Random	26.00			1.056	0.969	1.151	1.246	0.213
	28.00	11447.000	28.000	3.061	0.122	76.949	0.680	0.497
Random	28.00			3.061	0.122	76.949	0.680	0.497
	35.00	10543.000	35.000	1.005	0.062	16.184	0.004	0.997
Random	35.00			1.005	0.062	16.184	0.004	0.997
	36.00	10193.000	36.000	1.181	1.044	1.336	2.652	0.008
Random	36.00			1.181	1.044	1.336	2.652	0.008
	45.00	10519.000	45.000	0.331	0.013	8.195	-0.676	0.499
Random	45.00			0.331	0.013	8.195	-0.676	0.499
	46.00	10249.000	46.000	0.969	0.793	1.183	-0.313	0.754
	46.00	11156.000	46.000	3.000	0.118	76.235	0.666	0.506
	46.00	11425.000	46.000	1.153	0.071	18.652	0.100	0.920
Random	46.00			0.974	0.798	1.188	-0.263	0.792
	47.00	10249.000	47.000	0.915	0.747	1.120	-0.863	0.388
Random	47.00			0.915	0.747	1.120	-0.863	0.388
	56.00	10251.000	56.000	1.030	0.294	3.613	0.046	0.963
	56.00	10309.000	56.000	0.638	0.313	1.299	-1.239	0.215
Random	56.00			0.717	0.386	1.331	-1.055	0.291
	58.00	10512.000	58.000	0.679	0.458	1.006	-1.929	0.054
Random	58.00			0.679	0.458	1.006	-1.929	0.054
	67.00	10249.000	67.000	0.945	0.771	1.158	-0.549	0.583
Random	67.00			0.945	0.771	1.158	-0.549	0.583
	68.00	10236.000	68.000	0.840	0.657	1.074	-1.390	0.164
Random	68.00			0.840	0.657	1.074	-1.390	0.164



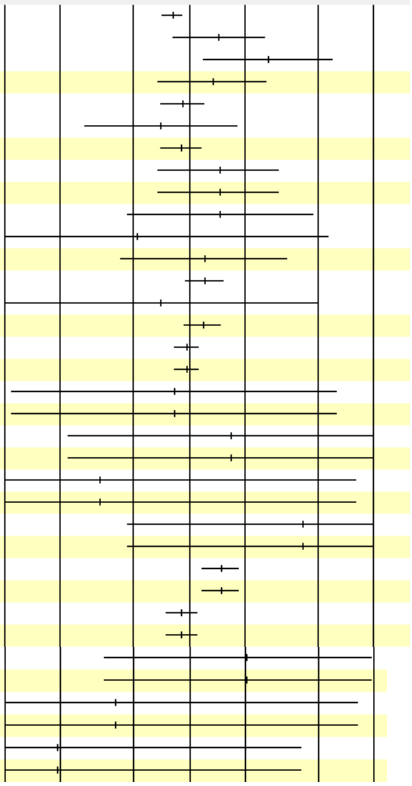
Sexual Dysfunction

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Group-A	Group-B
	110.00	12012.000	110.000	3.026	1.142	8.018	2.226	0.026	16 / 120	6 / 124
Random	110.00			3.026	1.142	8.018	2.226	0.026		
	12.00	10053.000	12.000	1.529	1.137	2.056	2.813	0.005	114 / 2365	76 / 2371
	12.00	10087.000	12.000	1.229	0.059	25.781	0.133	0.894	3 / 444	1 / 109
	12.00	10129.000	12.000	10.315	6.360	16.731	9.457	0.000	98 / 2238	20 / 4525
	12.00	10157.000	12.000	4.146	1.172	14.665	2.206	0.027	13 / 406	3 / 379
Random	12.00			3.454	0.899	13.268	1.805	0.071		
	13.00	10128.000	13.000	0.793	0.625	1.007	-1.904	0.057	128 / 3185	159 / 3172
	13.00	10129.000	13.000	5.039	2.993	8.485	6.084	0.000	50 / 2285	20 / 4525
	13.00	22095.000	13.000	2.976	1.466	6.042	3.019	0.003	31 / 156	12 / 156
Random	13.00			2.240	0.604	8.309	1.206	0.228		
	14.00	12012.000	14.000	1.356	0.456	4.030	0.548	0.583	8 / 124	6 / 124
Random	14.00			1.356	0.456	4.030	0.548	0.583		
	16.00	11510.000	16.000	0.530	0.096	2.935	-0.727	0.467	2 / 153	4 / 164
Random	16.00			0.530	0.096	2.935	-0.727	0.467		
	18.00	10162.000	18.000	3.671	2.371	5.683	5.830	0.000	93 / 508	29 / 504
	18.00	10170.000	18.000	1.043	0.065	16.802	0.030	0.976	1 / 186	1 / 194
Random	18.00			3.561	2.312	5.484	5.764	0.000		
	23.00	10129.000	23.000	0.489	0.346	0.690	-4.061	0.000	50 / 2285	98 / 2238
Random	23.00			0.489	0.346	0.690	-4.061	0.000		
	24.00	10388.000	24.000	1.427	0.676	3.010	0.934	0.351	17 / 707	12 / 707
Random	24.00			1.427	0.676	3.010	0.934	0.351		
	25.00	11039.000	25.000	0.647	0.012	33.577	-0.216	0.829	1 / 43	1 / 28
Random	25.00			0.647	0.012	33.577	-0.216	0.829		
	34.00	10187.000	34.000	0.772	0.688	0.865	-4.425	0.000	556 / 9639	707 / 9618
	34.00	10185.000	34.000	1.034	0.713	1.501	0.176	0.860	56 / 217	111 / 441
Random	34.00			0.845	0.648	1.102	-1.246	0.213		
	35.00	10221.000	35.000	0.755	0.613	0.929	-2.655	0.008	164 / 4605	214 / 4588
Random	35.00			0.755	0.613	0.929	-2.655	0.008		
	36.00	10185.000	36.000	1.249	0.928	1.682	1.466	0.143	129 / 436	111 / 441
Random	36.00			1.249	0.928	1.682	1.466	0.143		
	37.00	22074.000	37.000	2.461	0.965	6.272	1.886	0.059	25 / 152	6 / 81
Random	37.00			2.461	0.965	6.272	1.886	0.059		
	38.00	11447.000	38.000	1.000	0.135	7.392	0.000	1.000	2 / 50	2 / 50
	38.00	22074.000	38.000	1.493	0.493	4.523	0.708	0.479	8 / 75	6 / 81
Random	38.00			1.358	0.515	3.582	0.619	0.536		
	39.00	22074.000	39.000	1.705	0.576	5.043	0.964	0.335	9 / 75	6 / 81
Random	39.00			1.705	0.576	5.043	0.964	0.335		
	410.00	12012.000	410.000	2.231	0.917	5.427	1.769	0.077	16 / 120	8 / 124
Random	410.00			2.231	0.917	5.427	1.769	0.077		
	46.00	11156.000	46.000	0.333	0.013	8.471	-0.666	0.506	1 / 35	2 / 36
	46.00	10185.000	46.000	1.208	0.837	1.744	1.009	0.313	129 / 436	56 / 217
Random	46.00			1.188	0.825	1.712	0.928	0.354		
	48.00	10236.000	48.000	1.201	0.823	1.754	0.949	0.343	60 / 3164	50 / 3157
Random	48.00			1.201	0.823	1.754	0.949	0.343		
	49.00	10237.000	49.000	1.625	1.292	2.044	4.151	0.000	202 / 2666	126 / 2624
Random	49.00			1.625	1.292	2.044	4.151	0.000		
	56.00	11116.000	56.000	1.333	0.221	8.047	0.314	0.754	2 / 193	3 / 385
Random	56.00			1.333	0.221	8.047	0.314	0.754		
	78.00	22074.000	78.000	0.607	0.259	1.418	-1.154	0.249	8 / 75	25 / 152
Random	78.00			0.607	0.259	1.418	-1.154	0.249		
	79.00	22074.000	79.000	0.693	0.306	1.570	-0.880	0.379	9 / 75	25 / 152
Random	79.00			0.693	0.306	1.570	-0.880	0.379		
	89.00	22074.000	89.000	1.142	0.415	3.139	0.257	0.797	9 / 75	8 / 75
Random	89.00			1.142	0.415	3.139	0.257	0.797		



Depression

Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	12.00	10128.000	12.000	0.813	0.712	0.930	-3.026	0.002
	12.00	11114.000	12.000	1.459	0.816	2.608	1.275	0.202
	12.00	22095.000	12.000	2.682	1.193	6.028	2.387	0.017
Random	12.00			1.346	0.679	2.667	0.852	0.394
	13.00	10053.000	13.000	0.928	0.706	1.219	-0.538	0.591
	13.00	10087.000	13.000	0.705	0.271	1.833	-0.717	0.473
Random	13.00			0.909	0.699	1.182	-0.714	0.475
	16.00	10111.000	16.000	1.466	0.683	3.144	0.982	0.326
Random	16.00			1.466	0.683	3.144	0.982	0.326
	17.00	10170.000	17.000	1.478	0.461	4.742	0.657	0.511
	17.00	10172.000	17.000	0.519	0.047	5.771	-0.534	0.594
Random	17.00			1.212	0.424	3.461	0.359	0.720
	23.00	10100.000	23.000	1.211	0.954	1.536	1.576	0.115
	23.00	10145.000	23.000	0.703	0.098	5.058	-0.350	0.726
Random	23.00			1.201	0.949	1.521	1.523	0.128
	24.00	10221.000	24.000	0.967	0.831	1.125	-0.439	0.661
Random	24.00			0.967	0.831	1.125	-0.439	0.661
	26.00	22074.000	26.000	0.836	0.109	6.427	-0.172	0.863
Random	26.00			0.836	0.109	6.427	-0.172	0.863
	27.00	22074.000	27.000	1.705	0.220	13.184	0.511	0.609
Random	27.00			1.705	0.220	13.184	0.511	0.609
	28.00	22074.000	28.000	0.330	0.013	8.200	-0.677	0.499
Random	28.00			0.330	0.013	8.200	-0.677	0.499
	35.00	10251.000	35.000	4.180	0.463	37.720	1.274	0.203
Random	35.00			4.180	0.463	37.720	1.274	0.203
	57.00	10236.000	57.000	1.493	1.182	1.886	3.360	0.001
Random	57.00			1.493	1.182	1.886	3.360	0.001
	58.00	10237.000	58.000	0.917	0.748	1.123	-0.837	0.402
Random	58.00			0.917	0.748	1.123	-0.837	0.402
	67.00	22074.000	67.000	2.040	0.347	11.996	0.789	0.430
Random	67.00			2.040	0.347	11.996	0.789	0.430
	68.00	22074.000	68.000	0.394	0.019	8.304	-0.598	0.550
Random	68.00			0.394	0.019	8.304	-0.598	0.550
	78.00	22074.000	78.000	0.193	0.009	4.085	-1.056	0.291
Random	78.00			0.193	0.009	4.085	-1.056	0.291



Appendix 4:
Summary of Model Fit Statistics from Network Meta-Analyses

The adequacy of statistical fit for a given model can be established by comparing the number of data points in the data set to the residual deviance for the corresponding analysis; approximately a 1-1 ratio should be present. To compare the fit of competing models, their deviance information criteria values can be compared. We consistently used random effects consistency models over fixed effects consistency models based on our findings given that they were typically associated with similar or improved DIC values and random effects models are more justifiable.

Summary of Model fit Statistics from Primary Network Meta-Analyses, both Consistency and Inconsistency Models				
Outcome	**# unconstrained data points**	**FE consistency model fit (residual deviance; DIC)**	**RE consistency model fit (residual deviance; DIC)**	**RE inconsistency model fit (residual deviance; DIC)**
Overall mortality	133	137.7; 807.6	135.1; 808.4	138.2; 810.3
Cardiovascular mortality	86	95.9; 560.5	81.3; 552.9	81.3; 552.8
All stroke	78	123.1; 577.1	79.7; 548.5	81.7; 551.4
All MI	59	108.8; 432.5	62.3; 398.8	57.2; 389.0
Cancer	52	44.4; 311.6	44.8; 313.7	45.7; 314.5
Incident diabetes	54	90.6; 429.7	52.3; 391.0	52.8; 397.4
Depression	32	39.3; 213.7	31.2; 210.3	31.3; 210.5
Sexual dysfunction	47	139.9; 383.3	43.5; 296.8	47.3; 304.4

Appendix 5:
Summary of Findings from Network Meta-Regression Analyses and Subgroup Analyses

The following series of tables provides a comparison of each of the active treatments against the control treatment (placebo/no treatment) obtained from both the primary analyses based on random effects network meta-analysis as well as an additional random effects meta-regression model for network meta-analysis adjusting for different variables (year of study publication, control group risk,% female participants, mean age, use of prior antihypertensive medications, industry funding) as sensitivity analyses. We also include tables summarizing findings from subgroup analyses related to patient risk (lower risk versus moderate/high). For brevity, not all possible pairwise comparisons are reported. The tables include summary estimates for all treatments included in our treatment networks. All estimates are reported as summary odds ratios with corresponding 95% credible intervals. Model fit statistics are also provided.

Note: the following abbreviations are used in the following tables: BB=beta blockers, TZD=thiazide diuretics, ACE-I=ACE inhibitors, CCB= calcium channel blockers, ARB=angiotensin receptor blockers.

Summary of Findings from Network Meta-Regressions, Overall Mortality							
Treatment vs control group	**Unadjusted model**	**Adjusted for control group risk**	**Adjusted for publication year**	**Adjusted for mean age**	**Adjusted for % males**	**Adjusted for industry funding**	**Adjusted for background therapy**
BB	0.99 (0.9 - 1.08)	1.01 (0.91 - 1.12)	0.99 (0.9 - 1.08)	0.98 (0.9 - 1.08)	0.98 (0.88 - 1.08)	0.92 (0.81 - 1.05)	0.97 (0.87 - 1.07)
TZD	0.91 (0.84 - 0.99)	0.94 (0.85 - 1.03)	0.91 (0.84 - 0.99)	0.91 (0.83 - 0.99)	0.9 (0.82 - 0.99)	0.87 (0.78 - 0.96)	0.89 (0.81 - 0.99)
ACE-I	0.93 (0.83 - 1.03)	0.96 (0.84 - 1.08)	0.93 (0.82 - 1.03)	0.92 (0.81 - 1.02)	0.92 (0.81 - 1.03)	0.88 (0.77 - 0.99)	0.9 (0.79 - 1.02)
CCB	0.91 (0.83 - 0.98)	0.93 (0.84 - 1.03)	0.9 (0.83 - 0.99)	0.9 (0.82 - 0.98)	0.9 (0.82 - 0.98)	0.85 (0.76 - 0.95)	0.88 (0.79 - 0.98)
ARB	0.9 (0.82 - 1)	0.93 (0.81 - 1.05)	0.9 (0.8 - 0.99)	0.9 (0.8 - 1)	0.89 (0.79 - 0.99)	0.83 (0.72 - 0.97)	0.88 (0.78 - 0.99)
BB+TZD	0.88 (0.74 - 1.02)	0.91 (0.76 - 1.07)	0.88 (0.74 - 1.02)	0.87 (0.73 - 1.02)	0.87 (0.72 - 1.02)	0.83 (0.71 - 0.98)	0.86 (0.71 - 1.01)
TZD+other	0.73 (0.61 - 0.89)	0.75 (0.62 - 0.91)	0.74 (0.6 - 0.88)	0.73 (0.59 - 0.88)	0.73 (0.6 - 0.88)	0.69 (0.58 - 0.84)	0.72 (0.59 - 0.87)
BB+other	0.88 (0.71 - 1.12)	0.9 (0.72 - 1.14)	0.89 (0.7 - 1.11)	0.88 (0.7 - 1.11)	0.88 (0.69 - 1.11)	0.83 (0.65 - 1.05)	0.87 (0.68 - 1.1)
Other trts	0.97 (0.55 - 1.73)	0.99 (0.53 - 1.79)	1.01 (0.56 - 1.84)	1.02 (0.51 - 1.86)	0.96 (0.47 - 1.77)	0.94 (0.54 - 1.63)	0.97 (0.51 - 1.75)
Residual deviance	135.1	136	134.9	135.0	134.8	134.0	134.8
DIC	808.4	810.3	811.8	812.6	812.1	809.4	812.1
# data points	133	133	133	133	133	133	133
Beta	NA	-0.05 (-0.16, 0.06)	0.002 (-0.01, 0.01)	0.01 (-0.01, 0.01)	-0.13 (-0.63, 0.32)	0.10 (-0.04, 0.25)	0.05 (-0.08, 0.19)
SD	0.04	0.04	0.04	0.05	0.04	0.03	0.05

NA=not applicable; SD=standard deviation; DIC=deviance information criteria

Overall Mortality: Summary of Findings from Network Meta-Analysis, moderate/high risk versus lesser risk patients			
Treatment vs control group	**All patients**	**Moderate/High Risk**	**Lesser Risk**
BB	0.99 (0.9 - 1.08)	1.01 (0.91 - 1.13)	0.95 (0.68 - 1.32)
TZD	0.91 (0.84 - 0.99)	0.9 (0.82 - 0.99)	0.98 (0.7 - 1.32)
ACE-I	0.93 (0.83 - 1.03)	0.93 (0.82 - 1.04)	0.28 (0 - 14.42)
CCB	0.91 (0.83 - 0.98)	0.91 (0.83 - 1)	1.34 (0.4 - 4.95)
ARB	0.9 (0.82 - 1)	0.91 (0.82 - 1.01)	No data
BB+TZD	0.88 (0.74 - 1.02)	0.88 (0.74 - 1.04)	No data
TZD+other	0.73 (0.61 - 0.89)	0.76 (0.62 - 0.93)	0.39 (0.17 - 0.98)
BB+other	0.88 (0.71 - 1.12)	0.89 (0.7 - 1.12)	No data
Other trts	0.97 (0.55 - 1.73)	0.96 (0.5 - 1.77)	6.30 (0.21 - 18230)
Residual deviance	135.1	108.3	27.2
DIC	808.4	666.1	152.2
# data points	133	99	27

NA=not applicable; DIC=deviance information criteria

Summary of Findings from Network Meta-Regressions, Cardiovascular Mortality							
Treatment vs control group	**Unadjusted model**	**Adjusted for control group risk**	**Adjusted for publication year**	**Adjusted for mean age**	**Adjusted for % males**	**Adjusted for industry funding**	**Adjusted for background therapy**
BB	0.97 (0.83 - 1.12)	0.98 (0.83 - 1.14)	0.96 (0.82 - 1.12)	0.96 (0.81 - 1.13)	0.97 (0.81 - 1.13)	0.87 (0.71 - 1.07)	0.96 (0.8 - 1.15)
TZD	0.87 (0.77 - 1)	0.88 (0.77 - 1.01)	0.87 (0.77 - 1)	0.87 (0.75 - 1)	0.87 (0.75 - 1)	0.82 (0.71 - 0.96)	0.87 (0.74 - 1.01)
ARBs	0.92 (0.78 - 1.08)	0.92 (0.78 - 1.09)	0.87 (0.73 - 1.03)	0.9 (0.76 - 1.09)	0.91 (0.76 - 1.09)	0.8 (0.63 - 1.01)	0.91 (0.74 - 1.11)
ACE-I	0.9 (0.73 - 1.11)	0.91 (0.73 - 1.13)	0.88 (0.72 - 1.09)	0.88 (0.7 - 1.11)	0.89 (0.71 - 1.11)	0.83 (0.66 - 1.04)	0.89 (0.7 - 1.13)
CCB	0.87 (0.75 - 1)	0.88 (0.75 - 1.02)	0.85 (0.73 - 0.98)	0.86 (0.73 - 1.01)	0.87 (0.74 - 1.01)	0.79 (0.65 - 0.95)	0.86 (0.71 - 1.03)
BB+TZD	0.81 (0.62 - 1.03)	0.83 (0.62 - 1.05)	0.81 (0.63 - 1.03)	0.8 (0.6 - 1.02)	0.8 (0.59 - 1.03)	0.76 (0.58 - 0.96)	0.8 (0.6 - 1.03)
BB+other	0.75 (0.53 - 1.07)	0.76 (0.53 - 1.09)	0.73 (0.51 - 1.04)	0.74 (0.51 - 1.08)	0.75 (0.51 - 1.08)	0.68 (0.47 - 0.99)	0.74 (0.5 - 1.09)
TZD+other	0.65 (0.51 - 0.81)	0.67 (0.51 - 0.88)	0.66 (0.52 - 0.83)	0.64 (0.5 - 0.8)	0.64 (0.5 - 0.82)	0.62 (0.49 - 0.78)	0.64 (0.5 - 0.81)
Residual deviance	81.3	82.1	86.9	81.6	81.4	80.5	81.4
DIC	552.9	554.8	551.4	554.4	554.6	552.0	554.3
# data points	86	86	86	86	86	86	86
Beta	NA	-0.05 (-0.22, 0.13)	0.01 (-0.01, 0.02)	0.002 (-0.01, 0.01)	-0.04 (-0.71, 0.54)	0.17 (-0.05, 0.40)	0.02 (-0.20, 0.24)
SD	0.09	0.09	0.09	0.09	0.10	0.08	0.10

NA=not applicable; SD=standard deviation; DIC=deviance information criteria

Cardiovascular Mortality: Summary of Findings from Network Meta-Analysis, moderate/high risk versus lesser risk patients			
Treatment vs control group	**All patients**	**Moderate/High Risk**	**Lesser Risk**
BB	0.97 (0.83 - 1.12)	1.06 (0.9 - 1.25)	0.63 (0.13 - 2.07)
TZD	0.87 (0.77 - 1)	0.84 (0.73 - 0.97)	0.93 (0.28 - 2.1)
ARBs	0.92 (0.78 - 1.08)	0.95 (0.81 - 1.12)	No data
ACE-I	0.90 (0.73 - 1.11)	0.91 (0.74 - 1.12)	No data
CCB	0.87 (0.75 - 1)	0.91 (0.78 - 1.05)	1.15 (0.09 - 11.62)
BB+TZD	0.81 (0.62 - 1.03)	0.84 (0.65 - 1.05)	No data
BB+other	0.75 (0.53 - 1.07)	0.79 (0.56 - 1.11)	No data
TZD+other	0.65 (0.51 - 0.81)	0.66 (0.53 - 0.84)	0.41 (0.06 - 2.75)
Residual deviance	81.3	65.6	14.9
DIC	552.9	464.3	90.9
# data points	85	70	15

NA=not applicable; DIC=deviance information criteria

Summary of Findings from Network Meta-Regressions, Stroke (fatal and non-fatal)							
Treatment vs control group	**Unadjusted model**	**Adjusted for control group risk**	**Adjusted for publication year**	**Adjusted for mean age**	**Adjusted for % males**	**Adjusted for industry funding**	**Adjusted for background therapy**
BB	0.86 (0.68 - 1.07)	0.87 (0.7 - 1.06)	0.89 (0.73 - 1.1)	0.85 (0.66 - 1.06)	0.87 (0.68 - 1.08)	0.87 (0.62 - 1.2)	0.73 (0.52 - 0.99)
TZD	0.67 (0.54 - 0.81)	0.65 (0.54 - 0.78)	0.71 (0.58 - 0.85)	0.65 (0.52 - 0.79)	0.67 (0.54 - 0.81)	0.67 (0.52 - 0.84)	0.58 (0.42 - 0.75)
ACE-I	0.85 (0.62 - 1.11)	0.78 (0.59 - 1.02)	0.85 (0.65 - 1.1)	0.82 (0.6 - 1.09)	0.85 (0.62 - 1.11)	0.86 (0.6 - 1.15)	0.71 (0.47 - 1.01)
CCB	0.68 (0.54 - 0.84)	0.66 (0.53 - 0.81)	0.66 (0.54 - 0.81)	0.66 (0.51 - 0.82)	0.68 (0.54 - 0.85)	0.69 (0.5 - 0.92)	0.57 (0.4 - 0.77)
ARB	0.72 (0.54 - 0.94)	0.72 (0.56 - 0.91)	0.66 (0.5 - 0.84)	0.69 (0.51 - 0.91)	0.73 (0.54 - 0.96)	0.74 (0.48 - 1.08)	0.62 (0.43 - 0.86)
BB+TZD	0.76 (0.5 - 1.12)	0.72 (0.48 - 1.02)	0.81 (0.56 - 1.16)	0.73 (0.47 - 1.09)	0.78 (0.5 - 1.14)	0.77 (0.49 - 1.16)	0.67 (0.42 - 1.02)
TZD+other	0.41 (0.25 - 0.66)	0.41 (0.25 - 0.61)	0.48 (0.3 - 0.75)	0.41 (0.24 - 0.66)	0.41 (0.24 - 0.65)	0.42 (0.24 - 0.67)	0.37 (0.21 - 0.6)
BB+other	0.83 (0.47 - 1.45)	0.81 (0.49 - 1.32)	0.81 (0.49 - 1.34)	0.81 (0.44 - 1.43)	0.84 (0.47 - 1.45)	0.85 (0.45 - 1.54)	0.7 (0.37 - 1.26)
Residual deviance	79.7	80.5	77.7	78.6	80.9	80.0	78
DIC	548.5	547.2	545.3	548.2	550.0	549.6	547.2
# data points	78	78	78	78	78	78	78
Beta	NA	0.21 (-0.01, 0.42)	0.02 (0.01, 0.04)	0.01 (-0.01, 0.03)	0.25 (-0.82, 1.14)	-0.03 (-0.38, 0.37)	0.25 (-0.07, 0.58)
SD	0.23	0.19	0.20	0.24	0.22	0.24	0.23

NA=not applicable; SD=standard deviation; DIC=deviance information criteria

Stroke, Summary of Findings from Network Meta-Analysis, moderate/high risk versus lesser risk patients			
Treatment vs control group	**All patients**	**Moderate/High Risk**	**Lesser Risk**
BB	0.86 (0.68 - 1.07)	0.95 (0.74 - 1.22)	0.58 (0.09 - 1.96)
TZD	0.67 (0.54 - 0.81)	0.74 (0.60 - 0.91)	0.43 (0.09 - 1.49)
ACE-I	0.85 (0.62 - 1.11)	0.91 (0.68 - 1.16)	4.83 (0.08 - 4073)
CCB	0.68 (0.54 - 0.84)	0.73 (0.58 - 0.89)	0.34 (0.01 - 6.81)
ARB	0.72 (0.54 - 0.94)	0.75 (0.59 - 0.97)	NA
BB+TZD	0.76 (0.5 - 1.12)	0.82 (0.55 - 1.16)	NA
TZD+other	0.41 (0.25 - 0.66)	0.52 (0.31 - 0.84)	0.22 (0.01 - 3.30)
BB+other	0.83 (0.47 - 1.45)	0.89 (0.53 - 1.47)	NA
Residual deviance	79.7	55.6	20.9
DIC	548.5	434.1	115.5
# data points	78	59	19

Summary of Findings from Network Meta-Regressions, Myocardial Infarction (fatal and non-fatal)							
Treatment vs control group	**Unadjusted model**	**Adjusted for control group risk**	**Adjusted for publication year**	**Adjusted for mean age**	**Adjusted for % males**	**Adjusted for industry funding**	**Adjusted for background therapy**
BB	0.94 (0.73 - 1.2)	0.94 (0.72 - 1.23)	0.93 (0.69 - 1.24)	0.94 (0.73 - 1.21)	0.96 (0.74 - 1.24)	0.81 (0.49 - 1.38)	0.95 (0.69 - 1.29)
TZD	0.75 (0.57 - 0.99)	0.76 (0.57 - 1.01)	0.75 (0.55 - 1.02)	0.75 (0.57 - 1)	0.77 (0.58 - 1.05)	0.66 (0.4 - 1.11)	0.76 (0.55 - 1.06)
CCB	0.89 (0.68 - 1.13)	0.89 (0.67 - 1.15)	0.89 (0.68 - 1.13)	0.88 (0.68 - 1.13)	0.89 (0.68 - 1.15)	0.78 (0.48 - 1.27)	0.9 (0.62 - 1.27)
ARB	1.05 (0.77 - 1.42)	1.05 (0.76 - 1.44)	1.06 (0.76 - 1.49)	1.05 (0.75 - 1.45)	1.08 (0.78 - 1.52)	0.9 (0.51 - 1.62)	1.06 (0.72 - 1.55)
ACE-I	0.66 (0.47 - 0.91)	0.67 (0.47 - 0.93)	0.66 (0.47 - 0.93)	0.66 (0.47 - 0.93)	0.67 (0.48 - 0.94)	0.58 (0.34 - 1)	0.67 (0.45 - 0.98)
BB+TZD	0.74 (0.44 - 1.21)	0.75 (0.44 - 1.25)	0.74 (0.43 - 1.24)	0.74 (0.44 - 1.24)	0.75 (0.44 - 1.25)	0.65 (0.33 - 1.26)	0.75 (0.42 - 1.31)
BB+other	0.75 (0.42 - 1.29)	0.75 (0.41 - 1.34)	0.75 (0.41 - 1.32)	0.75 (0.41 - 1.31)	0.75 (0.42 - 1.33)	0.66 (0.33 - 1.33)	0.76 (0.4 - 1.41)
TZD+other	0.94 (0.29 - 2.95)	0.93 (0.28 - 3.16)	0.91 (0.25 - 3.36)	0.98 (0.29 - 3.29)	0.95 (0.28 - 3.2)	0.96 (0.28 - 3.34)	0.97 (0.29 - 3.13)
Other	0.17 (0 - 5.02)	0.13 (0 - 4.57)	0.12 (0 - 4.55)	0.13 (0 - 5.17)	0.14 (0 - 4.92)	0.1 (0 - 3.3)	0.13 (0 - 4.44)
Residual deviance	56.4	56.9	55.3	55.5	55.1.1	55.6	55.5
DIC	388.5	389.9	389.7	390.0	389.4	390.1	389.6
# data points	59	59	59	59	59	59	59
Beta	NA	-0.03 (-0.33, 0.28)	-0.003 (-0.03, 0.02)	0.0 (-0.02, 0.02)	0.53 (-1.03, 2.14)	0.16 (-0.38, 0.69)	-0.02 (-0.42, 0.38)
SD	0.21	0.22	0.22	0.22	0.22	0.21	0.22

NA=not applicable; SD=standard deviation; DIC=deviance information criteria

Myocardial Infarction: Summary of Findings from Network Meta-Analysis, moderate/high risk versus lesser risk patients			
Treatment vs control group	**All patients**	**Moderate/High Risk**	**Lesser Risk**
BB	0.94 (0.73 - 1.2)	0.76 (0.39 - 1.38)	An analysis in this subgroup was not performed; few trials reporting MI data were available for this population.
TZD	0.75 (0.57 - 0.99)	0.68 (0.39 - 1.25)	
CCB	0.89 (0.68 - 1.13)	0.95 (0.57 - 1.59)	
ARB	1.05 (0.77 - 1.42)	1.09 (0.59 - 2.04)	
ACE-I	0.66 (0.47 - 0.91)	0.62 (0.32 - 1.15)	
BB+TZD	0.74 (0.44 - 1.21)	0.74 (0.26 - 2.12)	
BB+other	0.75 (0.42 - 1.29)	0.80 (0.25 - 2.60)	
TZD+other	0.94 (0.29 - 2.95)	0.13 (0 - 5.40)	
Other	0.17 (0 - 5.02)	0.10 (0 - 4.42)	
Residual deviance	56.4	53.9	NA
DIC	388.5	347.4	NA
# data points	59	50	NA

NA=not applicable; SD=standard deviation; DIC=deviance information criteria

Appendix 6: Data Elements for Economic Evaluation

Parameter	Values	Source
Age-gender Specific Annual Cardiovascular risk	0.02-0.032	McCormack et al. 1997
Annual risk of heart failure	0.01	National Collaborating Centre for Chronic Conditions. 2006
Annual risk of diabetes	0.011	National Collaborating Centre for Chronic Conditions. 2006
Distribution of primary cardiovascular event by event type	age-specific	National Collaborating Centre for Chronic Conditions. 2006
Unstable angina		
Myocardial infarction		
Cardiovascular death		
Stroke		
Other		
Age specific non-cardiovascular death	age-specific	Statistics Canada 2010
Annual rates of events after event		
Event post Unstable Angina		National Collaborating
Myocardial Infarction	0.03	Centre for Chronic
Diabetes	0.00667	Conditions. 2006
Stroke	0.0095	
Heart Failure	0.023	
Cardiovascular Death	0.02	
Event post Myocardial Infarction		National Collaborating
Unstable Angina	0.00775	Centre for Chronic
Myocardial Infarction	0.0721	Conditions. 2006, Yusuf et
Diabetes	0.00667	al. 2000
Stroke	0.0095	
Heart Failure	0.023	
Cardiovascular Death	0.011	
Event post Stroke		National Collaborating
Unstable Angina	0.0016	Centre for Chronic
Myocardial Infarction	0.0016	Conditions. 2006, SOLVD
Diabetes	0.00667	Investigators 1992
Stroke	0.2875	
Heart Failure	0.0115	
Cardiovascular Death	0.34	
Event post Heart Failure		National Collaborating
Unstable Angina	0.023	Centre for Chronic
Myocardial Infarction	0.023	Conditions. 2006
Diabetes	0.011	
Stroke	0.01025	

Heart Failure		0.0545	
Cardiovascular Death		0.062	
Utility Values			
Age-gender Specific Utility Values for No Event		0.695-0.861	Statistics Canada 2011
Event based utility weights			Tran et al. 2007
Myocardial Infarction		0.76	
Post Myocardial Infarction		0.88	
Unstable Angina		0.77	
Post Unstable Angina		0.8	
Stroke		0.63	
Diabetes		0.9	
Heart Failure		0.71	
Cost Data			
Event Costs			Goeree et al. 2007
Myocardial Infarction		$9,737.49	
Post Myocardial Infarction		$3,839.02	
Unstable Angina		$3,818.63	
Post Unstable Angina		$3,419.20	
Stroke		$19,877.17	
Post stroke		$5,095.19	
Diabetes		$3,228.57	
Post diabetes		$1,366.36	
Heart Failure		$12,248.17	
Post Heart Failure		$7,602.01	
Annual drug costs			Ontario Ministry of Health
TZD:	HCTZ 25mg	$41.51	and Long-Term Care. 2014.
ARB	valsartan 80mg	$151.92	
CCB	amlodipine 5mg	$130.60	
BB	metoprolol 50mg bid	$84.52	
ACE	ramipril 10mg	$108.72	
BB+TZD	metoprolol 50mg bid + HCTZ 25mg	$126.03	
TZD + ARB	Valsartan+HCT 160/12.5mg	$151.92	

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