# A SYSTEMATIC REVIEW OF THE BLOOD PRESSURE LOWERING EFFICACY OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS FOR PRIMARY HYPERTENSION

by

BALRAJ SINGH HERAN

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## ABSTRACT

**Context:** Although the long-term goal of antihypertensive therapy is to reduce adverse clinical outcomes, the only way to evaluate the efficacy of treatment in an individual is the magnitude of blood pressure (BP) reduction. ACE inhibitors and angiotensin receptor blockers (ARBs) are two drug classes that, by different mechanisms, inhibit the renin-angiotensin-aldosterone system that regulates BP. As these drugs are widely prescribed for hypertension, it is essential to determine and compare their effects on BP, heart rate and tolerability.

**Objectives:** 1) To determine the dose-related effect of ACE inhibitors and ARBs on BP, heart rate and withdrawals due to adverse effects (WDAE) compared with placebo in the treatment of primary hypertension (SBP ≥ 140 mm Hg and/or ≥ DBP 90 mm Hg); and 2) To compare the relative effect on BP, heart rate and WDAE of a) each ACE inhibitor with other ACE inhibitors, b) each ARB with other ARBs, and c) all ACE inhibitors with all ARBs.

**Methods:** Two systematic reviews of published, double-blind, randomized, controlled trials (RCTs) evaluating the BP lowering efficacy of fixed dose monotherapy with an ACE inhibitor or ARB compared with placebo for a duration of 3 to 12 weeks in patients with primary hypertension were conducted. Electronic databases were searched for RCTs and similar trial inclusion criteria and methods of analysis were used in both reviews.

**Results:** Ninety two RCTs evaluated the dose-related BP lowering efficacy of 14 ACE inhibitors in 12 954 participants with a baseline BP of 157.1/101.2 mm Hg. Forty six RCTs evaluated the dose-related BP lowering efficacy of 9 ARBs in 13 451 participants with a baseline BP of 155.6/101.0 mm Hg. The best estimate of the near maximal trough BP reduction for ACE inhibitors and ARBs was -8/-5 mm Hg and -8/-5 mm Hg, respectively. ACE inhibitors and ARBs do not affect heart rate. The evidence for short-term withdrawals due to adverse effects (tolerability) was incomplete and weak and did not demonstrate a difference between the two classes of drugs.

**Conclusion:** ACE inhibitors and ARBs are not different individually or as drug classes in BP lowering efficacy.

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| | |
|---|---|
| AI | angiotensin I |
| AII | angiotensin II |
| ACE | angiotensin-converting enzyme |
| ACEI | angiotensin-converting enzyme inhibitor |
| ARB | angiotensin receptor blocker |
| AT1 | angiotensin II type 1 receptor |
| AT2 | angiotensin II type 2 receptor |
| BP | blood pressure |
| bpm | beats per minute |
| CI | confidence interval |
| DBP | diastolic blood pressure |
| Max | manufacturer's maximum recommended daily dose |
| RAAS | renin-angiotensin-aldosterone system |
| RCT | randomized, controlled trial |
| RR | relative risk |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SE | standard error |
| t ½ | half-life |
| tmax | time to maximum concentration |
| WDAE | withdrawals due to adverse effects |

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*With all my heart,*

*Benji*

## CO-AUTHORSHIP STATEMENT

Dr. James M. Wright conceived the research program. For his systematic reviews, Balraj Heran adapted the research protocol of a systematic review of the blood pressure lowering efficacy of thiazide and loop diuretics for primary hypertension previously designed by Dr. Wright and Dr. Vijaya Musini. Balraj Heran designed the search strategy, undertook the search, screened search results, collected data for the review, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, wrote to authors of papers for additional information, entered data into the Review Manager software, analyzed and interpreted data, and prepared the manuscripts. Dr. Michelle Wong and Inderjit K. Heran independently verified the inclusion of studies and the accuracy of the data extracted by Balraj Heran. Through all stages of this research, Dr. Wright assisted with the analysis and interpretation of data, as well as provided a clinical perspective.

# 1 INTRODUCTION

## 1.1 Hypertension

Hypertension, or elevated blood pressure, is a surrogate marker and major risk factor for stroke, coronary artery disease, congestive heart failure and renal and peripheral vascular disease. Primary hypertension implies that there is no known cause and comprises over 90% of hypertensive patients. Hypertension guidelines differ with respect to the blood pressure thresholds for which initiation of anti-hypertensive therapies is recommended [1]. Thus the numerical criteria used to define normotension and hypertension are arbitrary and subject to change as new evidence regarding treatment of hypertension becomes available. It is important to individualize the diagnosis and treatment of hypertension, which is more practically defined as that level of blood pressure above which investigation and treatment do more good than harm [2].

## 1.2 Management and treatment of primary hypertension

The goal of any antihypertensive therapy is to lower the risk of morbidity and mortality outcomes associated with elevated blood pressure. Systematic reviews of major clinical trials evaluating morbidity and mortality outcomes have demonstrated clear benefits of antihypertensive therapy in reducing cardiac and cerebrovascular events [3,4]. Although the long-term goal of any antihypertensive therapy is to lower the risk of adverse clinical outcomes, the only way to evaluate the efficacy of treatment in the short term is the magnitude of blood pressure reduction. Thus, when studying a class of drugs, it is essential to know the dose-related blood pressure lowering effect.

## 1.3 The role of the renin-angiotensin-aldosterone system in BP regulation

The renin-angiotensin-aldosterone system (RAAS) plays a vital role in cardiovascular homeostasis, including blood pressure and mineral balance [5]. It is also a well-known fact that excess activation of this system contributes to the elevation of blood pressure in some situations. Activation of the RAAS results in increased production of angiotensin I (AI), which is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE). AII is a potent vasoconstrictor and also stimulates aldosterone secretion, which

increases sodium and water retention [6]. AII and aldosterone are also implicated in other potentially deleterious effects on the cardiovascular system, including endothelial damage, sympathetic activation, collagen formation and decreased nitric oxide production [6]. Together, these effects put a strain on the heart, which can eventually lead to myocardial infarction or heart failure. With the understanding that the RAAS plays a vital role in the regulation of blood pressure, two drug classes, ACE inhibitors and angiotensin type I receptor blockers (ARBs), were developed to inhibit the RAAS and thus provide a potentially beneficial therapeutic approach for the treatment of hypertension.

### 1.4 Mechanism of action of ACE inhibitors

The discovery that the conversion of AI to the vasoactive peptide AII is enzymatically mediated by ACE led to the development of ACE inhibitors [7]. ACE inhibitors achieve their favorable effects by blocking the production of AII, thereby inhibiting its biological effects, such as enhanced vasoconstriction and excessive sodium and water retention. The favorable effect of ACE inhibitors may also be partly attributed to the fact that ACE is identical to another enzyme called kininase II that is responsible for kinin degradation. By retarding degradation of bradykinin, ACE inhibitors prolong its beneficial vasodilatory and antitrophic effects [8]. However, the accumulation of bradykinin in the lung probably causes the side effect of dry cough and possibly other side effects that force some patients to discontinue treatment with ACE inhibitors [9].

Initially, it was believed that ACE is the only enzyme that will catalyze the production of AII from AI. However, it is unclear how complete the blockade by ACE inhibitors is and if there is continuing angiotensin II formation during chronic treatment with ACE inhibitors [5]. Numerous studies have now shown that some patients on long-term treatment with ACE inhibitors eventually have AII levels return to pretreatment levels, demonstrating that the blockade of the RAAS by the ACE inhibitor is incomplete. This phenomenon is referred to as “ACE escape” and it may be the result of AII formation through non-ACE-dependent pathways. For example, chymase, a serine protease found in the human heart and other tissues, is able to form AII from AI and is

not blocked by ACE inhibitors [5]. The physiological significance of these non-ACE-dependent pathways for AII formation is not known at the present time.

### 1.5 Mechanism of action of ARBs

ARBs inhibit the binding of AII to the angiotensin II type 1 (AT1) receptor, which is believed to mediate the harmful cardiovascular effects of angiotensin II. ARBs are believed to provide a more effective means of blockade of the RAAS than is possible with ACE inhibitors because this blockade at the receptor level is independent of the pathway for AII formation [6]. In addition, this drug class allows the displaced AII to continue to bind to the angiotensin II type II (AT2) receptors that are not blocked by ARBs. Since AT2 receptors are believed to mediate favorable vasodilatory and anti-trophic effects, this unopposed stimulation of the AT2 receptors may confer a theoretical advantage with ARBs over ACE inhibitors [10]. Furthermore, ARBs may be better tolerated since they do not interfere with the degradation of bradykinin that is responsible for cough and possibly other side effects of ACE inhibitors.

### 1.6 The importance of BP lowering efficacy evidence in clinical decision making

Unfortunately, for most ACE inhibitors and ARBs, randomized controlled trials as compared to placebo demonstrating a reduction in mortality and morbidity are not available. Therefore, in the usual clinical setting where these drugs are used it is critical to know whether there are differences in the drugs in terms of their efficacy in lowering blood pressure. Manufacturers of ACE inhibitors and ARBs achieve regulatory approval by demonstrating a reduction in blood pressure as compared to placebo. For each drug, the manufacturer recommends a starting dose and several higher doses up to a maximal recommended dose. The implication is that the higher doses achieve a greater reduction in blood pressure and that the recommended dose ranges of the different drugs are approximately equivalent in blood pressure lowering efficacy. However, little is known about the dose-related blood pressure lowering efficacy of these drugs and a comprehensive systematic review designed to measure this has not been done. One example of the importance of doing this is that the cost of most ACE inhibitors increases with dose and it is unclear whether there is additional value in terms of added blood pressure lowering efficacy with the higher doses.

In reality, major differences in pharmacokinetic (Tables 1.1 - 1.2) and pharmaco-dynamic properties of drugs within a class likely result in clinically meaningful differences in the magnitude and duration of their blood pressure lowering effect.

**Table 1.1: Pharmacokinetic properties of ACE inhibitors [11]**

| Parent Drug<br>Active Metabolite | Bioavailability (%) | Protein Bound (%) | tmax (h) | t ½ (h) | Elimination (%) | |
|---|---|---|---|---|---|---|
| | | | | | Hepatic | Renal |
| Benazepril<br>Benazeprilat | 37 | 97.0<br>95.0 | 0.5-1<br>1-4 | 10-11 | 12 | 88 |
| Captopril | 40-67 | 70-80 | 1-1.5 | 2 | | |
| Cilazapril<br>Cilazaprilat | 15 | 99 | 2- 4 | 1.5<br>50 | <0.5 | 70 |
| Enalapril<br>Enalaprilat | | 99 | 4-6 | 1.3<br>11 | | |
| Fosinopril<br>Fosinoprilat | 15-24 | 95 | 2-6 | 11.5 | 50 | 50 |
| Imidapril<br>Imidaprilat | 14-19 | 98 | 2<br>9.3 | 1.7<br>14.8 | >1 | 70 |
| Lisinopril | 10-17 | 98 | 6 | 12 | <1 | 60 |
| Moexipril<br>Moexiprilat | 13 | 50 | 1.5 | 2-9 | 1<br>52 | 1<br>7 |
| Perindopril<br>Perindoprilat | 14-19 | 99 | 1<br>3-7 | 0.8-1<br>30-120 | <1 | ~75 |
| Quinapril<br>Quinaprilat | 13 | 99 | 2-24 | 2<br>25 | 40 | 60 |
| Ramipril<br>Ramiprilat | 8 | 99 | 4-6.5 | 2-4<br>9-18<br>>50 | 40 | 60 |
| Spirapril<br>Spiraprilat | ~30 | 98 | | 35 | 0.1 | 45 |
| Temocapril | 10-20 | >90 | | | 3 | 86 |
| Trandolapril<br>Trandolaprilat | 20-35 | | 0.7<br>2-4 | 16-24 | 67 | 33 |

In addition, there are reasons described above to suspect blood pressure lowering and other effects may differ between ACE inhibitors and ARBs, which could be important in choosing whether or not to prescribe an ACE inhibitor or an ARB for a patient.

**Table 1.2: Pharmacokinetic properties of ARBs [11]**

| Parent Drug Active Metabolite | Bioavailability (%) | Protein Bound (%) | $t_{max}$ (h) | $t_{1/2}$ (h) | Elimination (%) | |
|---|---|---|---|---|---|---|
| | | | | | Hepatic | Renal |
| Candesartan cilexitil | 15 | 99.5 | | 3-4 | | |
| Candesartan | | 99.5 | 2-5 | 6-13 | 67 | 33 |
| Eprosartan | 13 | 98.0 | 1-3 | 5-9 | 90 | 10 |
| Irbesartan | 60-80 | 90.0 | 1.3-3 | 11-18 | 80 | 20 |
| Losartan | 29-43 | 98.7 | 1-1.5 | 1-3 | 65 | 35 |
| EXP 3174 | | 99.8 | 3-6 | 5-10 | | |
| Olmesartan medoxomil | | | | | | |
| Olmesartan | 26 | 99.0 | 1-2 | 13 | 50-65 | 35-50 |
| Tasosartan | | 99.8 | 0.5 | 3-7 | | |
| Telmisartan | 30-60 | 99.5 | 0.5-1 | 21-38 | 98 | 2 |
| Valsartan | 10-35 | 95.0 | 2-4 | 6-10 | 80 | 20 |

## 1.7 Availability of ACE inhibitors and ARBs for lowering BP

The management of elevated blood pressure has major consequences for the health care system because of the high prevalence of elevated blood pressure and the high cost of drugs to lower blood pressure. ACE inhibitors and ARBs are two drug classes that are commonly prescribed in the management of elevated blood pressure.

Currently, there are ten ACE inhibitors and six ARBs approved for use in Canada [11]. When ACE inhibitors and ARBs are prescribed, the physician must decide between the available drugs and choose a starting dose. Ideally, this decision would be made on the basis of randomized controlled trials showing a reduction in mortality and morbidity. Unfortunately, that is seldom the case. As mentioned above, most antihypertensive drugs are approved for use based on evidence that they lower blood pressure. In fact there are

very few trials measuring mortality and morbidity in which ACE inhibitors or ARBs have been compared to placebo for the treatment of hypertension.

The most widely known ACE inhibitor study is the HOPE study published in 2000 [12]. In the HOPE study, patients (55 years of age or older) were randomly assigned to ramipril 10 mg daily or matching placebo for a mean duration of five years. At baseline, patients had to have had a previous cardiovascular event or have diabetes mellitus with at least one other cardiovascular risk factor. It was not necessary for the patients to have elevated blood pressure and patients with known left ventricular dysfunction or heart failure were excluded. Patients treated with ramipril were found to have a 22% relative risk reduction in the primary composite outcome of cardiovascular death, myocardial infarction and cardiac arrest as compared to the placebo group. Blood pressure in the ramipril group was reported to be 3/2 mm Hg less than in the patients treated with placebo. Three years later, the results of the EUROPA study were published [13]. Patients with stable coronary heart disease and no apparent heart failure were randomly assigned to perindopril 4 mg daily or matching placebo for a mean of 4.2 years. Patients treated with perindopril had a 21% relative risk reduction in the primary composite outcome of cardiovascular death, myocardial infarction and stroke as compared to placebo. Blood pressure was decreased by 5/2 mm Hg in these patients as compared to placebo. These results provide evidence of the effectiveness of ACE inhibitors for secondary prevention. However, because of the relatively small effect on blood pressure they have been interpreted as evidence that they are working primarily independently of their effect on blood pressure. This interpretation is controversial and has been challenged. At any rate, it remains unclear as to what the relevance of these trials is to the use of ACE inhibitors for primary prevention in patients with elevated blood pressure.

Mortality and morbidity evidence is not available for most ACE inhibitors and ARBs in the setting of the treatment of elevated blood pressure in patients without previous cardiovascular disease. It is therefore critical to know whether there are differences in the drugs in terms of the dose-related blood pressure lowering ability in this the most common clinical setting where they are used.

## 1.8 What is a systematic review?

Publications about health care interventions have increased so dramatically over the years that researchers, health care providers and policy makers can no longer keep up with the large and often contradictory literature [14]. In most cases, a narrative review is an unreliable source because it frequently provides an incomplete and biased summary of past research. It is usually written by experts who tend to focus on a subset of the evidence that supports their view. A narrative review is unscientific because it lacks formal tools to select, integrate and analyze research evidence and is impossible to replicate.

A systematic review is a scientific technique that summarizes, appraises, and communicates the results and implications of large quantities of information [15]. It can be purely qualitative or it can have a quantitative component referred to as a meta-analysis. A meta-analysis involves combining the quantitative data from individual studies and thus increasing the statistical power and precision of the estimate of the effect size [15].

A systematic review answers a specific clinical question, maximizes precision and minimizes bias and has the same rigor as primary scientific research. A pre-specified plan outlining the objectives, the search strategy for identifying potentially relevant trials, the criteria for inclusion and exclusion of trials, the appraisal of methodological quality of the included trials and the reporting of findings is explicitly documented by the review author to allow replication. This also allows the review methods used to be subject to critical appraisal. Although a systematic review requires much more time and effort than a narrative review, it provides the most reliable up-to-date evidence for answering clinically important questions as well as identifying new research hypotheses. In addition, a systematic review identifies the strengths and weaknesses in primary trials and establishes whether the findings are consistent and generalizable across populations and different treatments [14].

A systematic review is not immune to problems and limitations. It is a retrospective study and therefore subject to bias. Some biases, such as selection and observer bias, are minimized by having at least two independent reviewers selecting

studies and extracting the relevant data. Biases inherent in the primary literature, such as publication bias – which describes the tendency of positive-result studies to be more likely to be published (sometimes multiple times) than negative-results studies – can also be present. In a quantitative meta-analysis, this can lead to an overestimate of the true treatment effect. However, statistical methods to correct for this type of bias are available to provide a more accurate estimate of the true effect size. Despite these potential disadvantages, a systematic review is still the best available comprehensive retrospective summary of research evidence.

### 1.9 The Cochrane Collaboration

The Cochrane Collaboration (CC) is a global not-for-profit and independent organization dedicated to improving healthcare decision-making by preparing, maintaining and disseminating up-to-date reviews of randomized controlled trial (RCT) evidence, as well as other reliable sources when RCT evidence is not available. The major product of the CC is the Cochrane Database of Systematic Reviews, an electronic publication that is updated quarterly. In addition to the advantages of a systematic review stated above, a Cochrane review is prepared and published using the CC's Review Manager software, which facilitates the update of reviews by easily incorporating missed or newly published trials. This user friendly format continues to be developed through an ongoing process of consultation with its users. A study that compared Cochrane reviews with articles published in paper-based journals concluded that Cochrane reviews were conducted with greater methodological rigor and were more likely to be updated [16].

### 1.10 Shortcomings of currently available evidence

At the present time there has not been a systematic study to assess whether there are clinically meaningful differences in blood pressure lowering efficacy among individual drugs and whether the manufacturer's dose range recommendations are rational. Others have attempted to answer these questions with different objectives from ours. A systematic review of the blood pressure lowering efficacy of five classes of antihypertensive agents, including ACE inhibitors and ARBs, was published by Law and Wald [17]. The primary objective of this comprehensive analysis was to identify a combination of blood pressure lowering drugs that would achieve large reductions in

blood pressure with minimal adverse effects. The authors did not attempt to establish or compare the dose-related blood pressure lowering efficacy of each ACE inhibitor or ARB. Instead Law and Wald made the assumption that the lowest manufacturer-recommended dose – defined as a "standard dose" – was equivalent among the drugs within a class. Using this assumption, they estimated a placebo-corrected average reduction in blood pressure according to drug class and dose as a proportion of the standard dose. The average reductions in systolic and diastolic blood pressure for each drug class showed statistically significant heterogeneity, or greater variation than expected due to chance alone. The authors failed to explain the heterogeneity but one of their suggested explanations challenges their definition of a "standard dose". For these and other reasons there is reason to doubt the effect estimates of this meta-analysis.

Another meta-analysis comparing the antihypertensive efficacy of drugs in the ARB class was published by Conlin et al [18]. This meta-analysis was limited to only four of the eight ARBs currently available worldwide. The authors attempted to gain a better understanding of the comparative efficacy of these four ARBs by considering evidence from 43 published RCTs comparing the various ARBs with placebo, other classes of antihypertensive agents, and "head-to-head" trials comparing ARBs directly with each other. The efficacy data from these trials were pooled but no attempt was made to quantify the dose-related blood pressure lowering efficacy of ARB monotherapy. Conlin et al. limited their meta-analysis of placebo-controlled RCTs to those studies that evaluated the recommended starting dose. No other placebo-controlled trials that studied the efficacy of ARB monotherapy at higher doses were included in the analysis.

### 1.11 Aim of this systematic review

There is therefore a need for a comprehensive review of all placebo-controlled trials measuring the blood pressure lowering efficacy of ACE inhibitors and ARBs at all doses. It is also essential that this review be done as a Cochrane review and that it be regularly updated. These two classes of drugs represent two of the most widely prescribed classes of drugs in the world and much of the information about their blood pressure lowering efficacy has never been systematically reviewed.

In this thesis, the systematic review of the blood pressure lowering efficacy of ACE inhibitors is presented in Chapter 2 and the systematic review of the blood pressure lowering efficacy of ARBs is presented in Chapter 3. Chapter 4 provides a discussion of what we learned by comparing the results from these two systematic reviews.

## 1.12 References


1. McAlister FA, Campbell NRC, Zarkne K, Levine M, Graham ID. The management of hypertension in Canada: A review of current guidelines, their shortcomings and implications for the future. CMAJ 2001; 164(4):517-522.

2. Rose G. Epidemiology. In: Marshal AJ and Barrett DW, editors. The Hypertensive Patient. Kent, England: Pitman Medical; 1980. p. 1-21.

3. Wright JM, Lee CH, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? CMAJ 1999; 161(1):25-32.

4. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: A network meta-analysis. JAMA 2003; 289(19):2534-44.

5. Wolny A, Clozel J, Rein J, Mory P, Vogt P, Turino M, et al. Functional and biochemical analysis of angiotensin II forming pathways in the human heart. Circulation Research 1997; 80:219-27.

6. Erhardt LR. A review of the current evidence for the use of angiotensin receptor blockers in chronic heart failure. International Journal of Clinical Practice 2005; 59(5):571-8.

7. Kostis JB, Rain JJ, DeFelice EA, Barone JA, Deeker RG. Comparative clinical pharmacology of ACE-inhibitors. In: Kostis JB, DeFelice EA, editors. Angiotensin converting enzyme inhibitors. New York: Alan R, Liss, Inc.; 1987. p. 19-54.

8. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: Meta-analysis of randomized controlled trials. Journal of the American College of Cardiology 2002; 39:463-70.

9. McMurrary JJV, Pfeffer MA. Heart failure. Lancet 2005; 365:1877-89.

10. Azizi M, Menard J. Combined blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin II type 1 antagonists. Circulation 2004; 109:2492-9.

11. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [updated 2006 Feb 27; cited 2007 Dec 1]. Available from: www.e-cps.ca. Also available in paper copy from the publisher.

12. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on death from cardiovascular

causes, myocardial infarction, and stroke in high-risk patients. NEJM 2000; 342(3):145-53.

13. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003; 362:782-8.

14. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

15. Mulrow CD. Systematic reviews: Rationale for systematic reviews. BMJ 1994; 309:597-9.

16. Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, Moher D. Methodology and reports of systematic reviews and meta-analyses: A comparison of cochrane reviews with articles published in paper-based journals. JAMA 1998; 280(3): 278-180.

17. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomised trials. BMJ 2003; 326.(7404):1427.

18. Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, et al. Angiotensin II antagonists for hypertension: Are there differences in efficacy? American Journal of Hypertension 2000; 13:418-26.

# 2 BLOOD PRESSURE LOWERING EFFICACY OF ACE INHIBITORS FOR PRIMARY HYPERTENSION[1]

## 2.1 Protocol

The protocol for this systematic review was first published in Issue 2, 2002 of the Cochrane Library [1] to outline the scientific methods that would be employed. The methodology was based on the Cochrane Reviewers' Handbook [2] and on a previous systematic review that assessed the blood pressure lowering efficacy of thiazide and loop diuretics [3].

### 2.1.1 Objectives

**Primary objective:**

- To quantify the dose-related systolic and/or diastolic blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors versus placebo in the treatment of primary hypertension.

**Secondary objectives:**

- To determine the effects of ACE inhibitors on variability of blood pressure.
- To determine the effects of ACE inhibitors on pulse pressure.
- To quantify the dose-related effects of ACE inhibitors on heart rate.
- To quantify the dose-related effect of ACE inhibitors on withdrawals due to adverse effects.

### 2.1.2 Methodology

#### 2.1.2.1 Types of studies

Included studies must be RCTs and their design must meet the following criteria:

- double-blind
- random allocation to fixed dose ACE inhibitor monotherapy group(s) and a parallel placebo control group

[1] A version of this chapter has been accepted for publication. Heran, B.S., Wong, M.M.Y., Heran, I.K. and Wright, J.M. Blood pressure lowering efficacy of ACE inhibitors for primary hypertension.

- duration of follow-up of at least three weeks
- office blood pressure measurements at baseline (following washout) and at one or more time points between 3 and 12 weeks post-treatment

#### 2.1.2.2 Types of participants

Participants must have an office baseline blood pressure of at least 140 mm Hg systolic and/or a diastolic blood pressure of at least 90 mm Hg. Patients must not have creatinine levels greater than 1.5 times the normal level, thereby excluding patients with secondary hypertension due to renal failure. Participants who were taking medications that affect blood pressure other than the study medications were excluded. Participants were not restricted by age, gender, baseline risk or any other co-morbid conditions.

#### 2.1.2.3 Types of interventions

Monotherapy with any ACE inhibitor, including alacepril, altiopril, benazepril, captopril, ceronapril, cilazapril, delapril, derapril, enalapril, fosinopril, idapril, imidapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, and zofenopril.

Trials in which titration to a higher dose was based on blood pressure response were not eligible if the titration occurred before 3 weeks of treatment because dose-response relationships cannot be analyzed if patients within each randomized group are taking different doses. However, trials in which a response-dependent titration took place during or after the 3 to 12 week interval were eligible if pre-titration data were given. For forced titration trials, data from the lowest dose were extracted, provided this dose was given for a 3 to 12 week period.

#### 2.1.2.4 Types of outcome measures

**Primary:**

- Change from baseline in trough and/or peak systolic and diastolic blood pressure at 3 to 12 weeks, compared with placebo. If blood pressure measurements were available at more than one time within the accepted window, the weighted means of blood pressures taken in the 3 to 12 week range were used.

**Secondary:**

- Standard deviation of the change in blood pressure compared with placebo.
- Change in standard deviation of blood pressure compared with placebo.
- Change in pulse pressure compared with placebo.
- Change in heart rate compared with placebo.
- Number of patient withdrawals due to adverse effects compared with placebo.

### 2.1.3 Search strategy for identification of studies

To identify randomized, double-blind, placebo-controlled trials of ACE inhibitors, Medline (1966-present), EMBASE (1988-present), Cochrane Central Register of Controlled Trials (CENTRAL), and bibliographic citations were searched. Previously published meta-analyses on dose-response of ACE inhibitors, as well as narrative reviews, were used to help identify references to trials. No language restrictions were applied.

A modified, expanded version of the standard search strategy of the Cochrane Hypertension Group, with additional terms related to ACE inhibitors, was used to identify relevant articles [4].

#### 2.1.3.1 Search strategy used for Medline

1. randomized controlled trial.pt
2. randomized controlled trial$.mp
3. controlled clinical trial.pt
4. controlled clinical trial$.mp
5. random allocation.mp
6. exp double-blind method/
7. double-blind.mp
8. exp single-blind method/
9. single-blind.mp
10. or/1-9
11. ANIMALS.sh. not HUMAN.sh.
12. 10 not 11

13. clinical trial.pt
14. clinical trial$.mp
15. exp clinical trials/
16. (clin$ adj25 trial$).mp
17. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).mp
18. random$.mp
19. exp research design/
20. research design.mp
21. or/13-20
22. 21 not 11
23. 22 not 12
24. comparative stud$.mp
25. exp evaluation studies/
26. evaluation stud$.mp
27. follow-up stud$.mp
28. prospective stud$.mp
29. (control$ or prospectiv$ or volunteer$).mp
30. or/24-29
31. 30 not 11
32. 31 not (12 or 23)
33. 12 and 23 and 32
34. exp angiotensin-converting enzyme inhibitors/
35. angiotensin-converting enzyme inhibitor$.mp
36. alacepril.mp
37. altiopril.mp
38. benazepril.mp
39. captopril.mp
40. ceronapril.mp
41. cilazapril.mp
42. delapril.mp
43. derapril.mp

44. exp enalapril/
45. enalapril.mp
46. fosinopril.mp
47. idapril.mp
48. imidapril.mp
49. lisinopril.mp
50. moexipril.mp
51. moveltipril.mp
52. pentopril.mp
53. perindopril.mp
54. quinapril.mp
55. ramipril.mp
56. spirapril.mp
57. temocapril.mp
58. trandolapril.mp
59. zofenopril.mp
60. or/34-59
61. exp hypertension/
62. hypertension.mp
63. exp blood pressure/
64. blood presure.mp
65. or/61-64
66. 60 and 65
67. 33 and 66
68. placebo$.mp
69. 67 and 68

#### 2.1.3.2 Search strategy used for EMBASE

1. randomized controlled trial$.mp.
2. exp controlled clinical trials/
3. controlled clinical trial$.mp.

4. exp random allocation/
5. random allocation.mp.
6. double-blind.mp.
7. single-blind.mp.
8. or/1-7
9. exp animal/
10. 8 not 9
11. exp clinical trials/
12. clinical trial$.mp.
13. (clin$ adj25 trial$).mp.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
15. random$.mp.
16. exp research design/
17. research design.mp.
18. or/11-17
19. 18 not 9
20. 19 not 10
21. exp comparative study/
22. comparative stud$.mp.
23. exp evaluation studies/
24. evaluation stud$.mp.
25. exp follow up studies/
26. follow up stud$.mp.
27. prospective stud$.mp.
28. (control$ or prospectiv$ or volunteer$).mp.
29. or/21-28
30. 29 not 9
31. 30 not (10 or 20)
32. 10 and 20 and 31
33. exp angiotensin-converting enzyme inhibitors/
34. angiotensin-converting enzyme inhibitor$.mp.

35. alacepril.mp.
36. altiopril.mp.
37. benazepril.mp.
38. captopril.mp.
39. exp ceronapril/
40. ceronapril.mp.
41. cilazapril.mp.
42. delapril.mp.
43. derapril.mp.
44. enalapril.mp.
45. fosinopril.mp.
46. idapril.mp.
47. imidapril.mp.
48. lisinopril.mp.
49. moexipril.mp.
50. exp moveltipril/
51. pentopril.mp.
52. perindopril.mp.
53. quinapril.mp.
54. ramipril.mp.
55. spirapril.mp.
56. temocapril.mp.
57. trandolapril.mp.
58. zofenopril.mp.
59. or/33-58
60. exp hypertension/
61. hypertension.mp.
62. exp blood pressure/
63. blood pressure.mp.
64. or/60-63
65. 59 and 64

66. 32 and 65

67. placebo$.mp.

68. 66 and 67

### 2.1.4 Study selection

The databases listed above were searched using the updated search strategy to identify citations with potential relevance. The initial screen of these abstracts excluded articles whose titles and/or abstracts were clearly irrelevant. The full text of remaining articles was then retrieved (and translated into English where required) to assess whether the trials met the pre-specified inclusion criteria. The bibliographies of pertinent articles, reviews and texts were searched for additional citations. Two independent reviewers assessed the eligibility of the trials using a trial selection form (Appendix I). A third reviewer resolved discrepancies. Trials with more than one publication were counted only once.

### 2.1.5 Data extraction

Data were extracted independently by two reviewers using a standard form (Appendix II) and then cross-checked. If data were presented numerically (in tables or text) and graphically (in figures), the numeric data were preferred because of possible measurement error when estimating from graphs. All numeric calculations and extractions from graphs or figures were confirmed by a second reviewer.

The position of the patient during blood pressure measurement may affect the blood pressure lowering effect. However, in order not to lose valuable data, if only one position was reported, data from that position were extracted. When blood pressure measurement data are available in more than one position, data were extracted in accordance with the following order of preference: 1) sitting; 2) standing; and 3) supine.

In the case of missing information in the included studies, investigators were contacted (by email, letter and/or fax) to obtain the missing information.

In the case of missing values for standard deviation of the change in blood pressure or heart rate, the standard deviation was imputed based on the information in the same trial or from other trials using the same dose. The following hierarchy (listed from high to low preference) was used to impute standard deviation values:

1. Pooled standard deviation calculated either from the t-statistic corresponding to an exact p-value reported or from the 95% confidence interval of the mean difference between treatment group and placebo.
2. Standard deviation of change in blood pressure/heart rate from a different position than that of the blood pressure data/heart rate used.
3. Standard deviation of blood pressure/heart rate at the end of treatment.
4. Standard deviation of blood pressure/heart rate at the end of treatment measured from a different position than that of the blood pressure/heart rate data used.
5. Standard deviation of blood pressure/heart rate at baseline (except if this measure was used for entry criteria).
6. Weighted mean standard deviation of change in blood pressure/heart rate from other trials using the same class of drug (at any dose).

### 2.1.6 Quality assessment

The quality of all included trials was assessed by two independent reviewers using the following two approaches that are commonly utilized in systematic reviews.

#### 2.1.6.1 Cochrane assessment of allocation sequence concealment

The Cochrane Collaboration judges the quality of a study on the method of allocation concealment [5]. Each trial in the systematic review is assigned a grade of A, B, C, or D:

**Grade A: Adequate**

- Some approaches that are adequate include: centralized (eg. central office unaware of subject characteristics) or pharmacy-controlled randomization; pre-numbered or coded identical containers which are administered serially to participants; on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; sequentially numbered, sealed, opaque envelopes.

**Grade B: Unclear**

- Adequacy should be considered unclear when the allocation concealment approach is not reported in the study; for example: simply stating that a list or table was used; only specifying that sealed envelopes were used; or reporting an apparently adequate

concealment scheme along with other details that leads the reviewer to be suspicious.

**Grade C: Inadequate**

- Some approaches that are clearly inadequate include: alternation; the use of case record numbers; dates of birth; or any procedure that is transparent before allocation, such as an open list of random numbers.

**Grade D: Allocation concealment not used**

- Allocation concealment was not used to assess validity.

#### 2.1.6.2 Jadad quality scale

A simple 5-point scoring system where a score of 0-2 reflects low quality, a score of 3-4 indicates moderate quality and a score of 5 represents a high quality study [6]. It is summarised as follows:

- Was the study described as randomised? (1=yes; 0=no)
- Was the study described as double-blind? (1=yes; 0=no)
- Was there a description of withdrawals and dropouts? (1=yes; 0=no)
- Was the method of randomisation well described and appropriate? (1=yes; 0=no)
- Was the method of double-blinding well described and appropriate? (1=yes; 0=no)
- Deduct 1 point if methods for randomisation were inappropriate.
- Deduct 1 point if methods for blinding were inappropriate.

### 2.1.7 Data analysis and statistical considerations

Data synthesis and analyses were done using the Cochrane Review Manager software, RevMan 4.2.8. Data for changes from baseline in blood pressure and heart rate were combined using a weighted mean difference method. The withdrawals due to adverse effects were analyzed using relative risk, risk difference, and number needed to harm.

When possible, direct and indirect comparisons of effect sizes between doses were performed for each ACE inhibitor drug. In the direct method, only trials that randomized participants to different doses were included in the analysis. In the indirect method, an "adjusted indirect comparison" and the associated standard error were calculated using the method described by Bucher et al. (1997) [7,8].

A p value less than 0.05 ($p < 0.05$) was considered statistically significant for all comparisons. If there was statistically significant heterogeneity associated with an effect estimate, a random effects model was applied. This model provides a more conservative statistical comparison of the difference between ACE inhibitor treatment and placebo because a confidence interval around the effect estimate is wider than a confidence interval around a fixed effect estimate. If a statistically significant difference was still present using the random effects model, the fixed effect pooled estimate and confidence interval were reported because of the tendency of smaller trials, which are more susceptible to publication bias, to be overweighted with a random effects analysis.

When possible, subgroup analyses were used to examine the results for specific categories of participants. Possible subgroup analyses included:

- Race: black, white, other
- Age: children, adults, older people
- Baseline severity of hypertension: mild, moderate, severe

The robustness of the results was tested using several sensitivity analyses, including:

- Trials of high quality versus poor quality.
- Trials that are industry-sponsored versus non-industry sponsored.
- Trials that assess drug as primary drug of investigation versus trials that assess drug as comparator.
- Trials with blood pressure data measured in the sitting position versus other measurement positions.
- Trials with published standard deviations of blood pressure change versus imputed standard deviations.

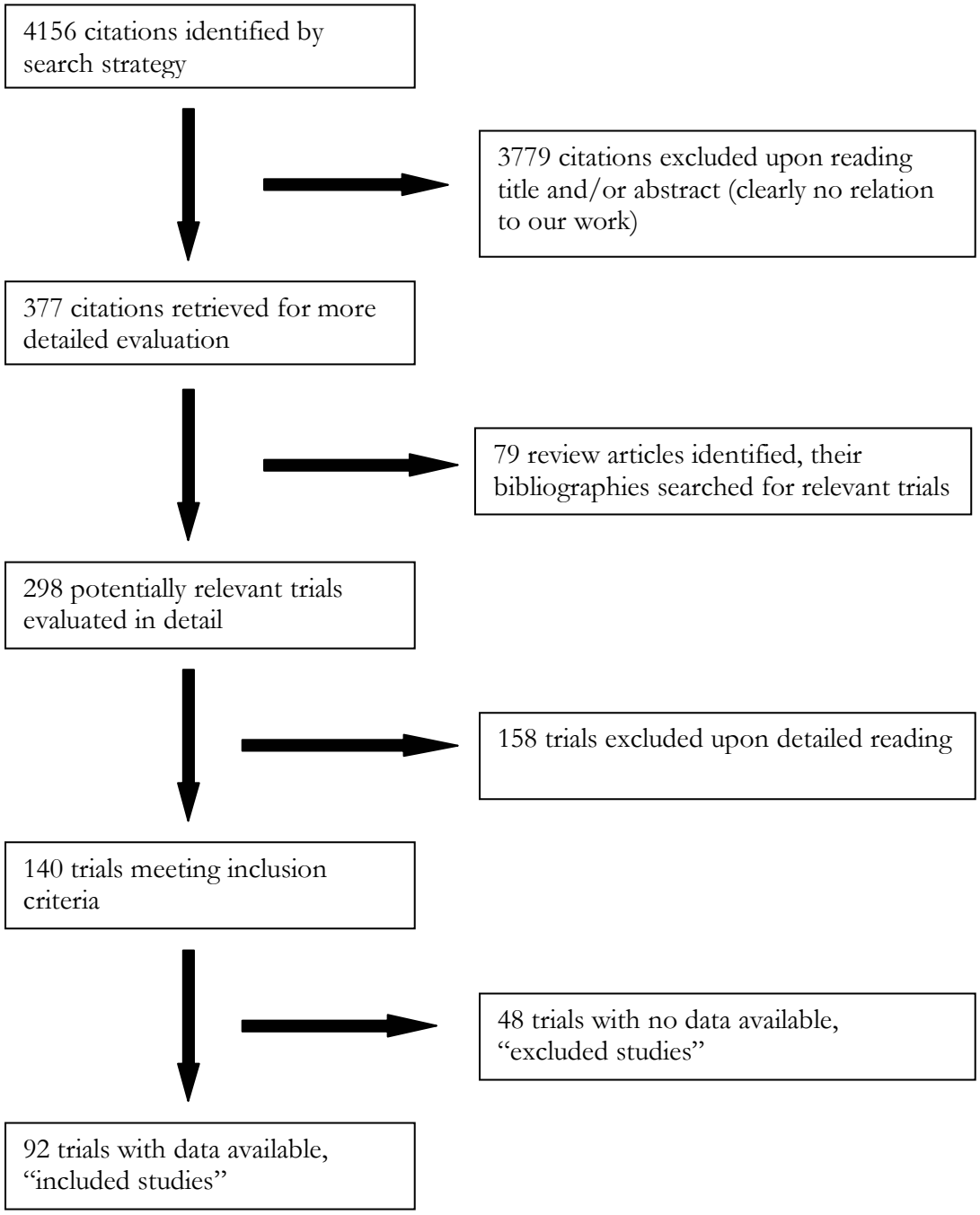
## 2.2 Results

### 2.2.1 Search findings

The search strategy identified 4156 citations, of which only 92 (2.2%) trials met the inclusion criteria and had extractable data to evaluate the dose-related blood pressure lowering efficacy of 14 ACE inhibitors (Figure 2.1). One hundred fifty eight studies were excluded because they did not meet the pre-specified inclusion criteria. An additional

forty eight trials met the inclusion criteria but did not have extractable data and therefore were excluded.

**Figure 2.1: QUOROM flow diagram**



#### 2.2.1.1 Characteristics of excluded studies

Forty eight studies that met the inclusion criteria were excluded from this review. Some of the reasons for exclusion were: failure to report adequate blood pressure data; the number of patients studied in each arm; crossover trials that did not report pre-crossover data; parallel group trials with a forced titration schedule; and trials in which patients were titrated to a pre-specified blood pressure response. Reasons for excluding each trial are listed in Table 2.1.

**Table 2.1: Reasons for exclusion of trials that met inclusion criteria**

| Study ID | Reason for exclusion |
|---|---|
| Bainbridge 1993 [9] | Crossover trial with no pre-crossover data for first 4 weeks of treatment (ramipril 2.5 mg/day vs. placebo). |
| Bakris 2002 [10] | Parallel group trial with 8-week treatment period, forced titration at 4 weeks. Pre-titration data not reported (enalapril 10 mg/day vs. losartan 50 mg/day vs. placebo). |
| Beaulieu 1993 [11] Duplicate publication: Beaulieu 1994 [12] | Crossover trial with no pre-crossover data for first 4 weeks of treatment (fosinopril 20 mg/day vs. placebo). |
| Bergstrand 1985 [13] | Balanced, two-period, incomplete-block design with 2 treatment periods of 3-weeks duration. First treatment period data not reported (enalapril 2.5, 5, 10, 20, 40 vs. placebo). |
| Bohlen 1996 [14] | Parallel group trial with 6-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (perindopril 4 mg/day vs. placebo). |
| Canter 1994 [15] | Parallel group trial with 8-week treatment period. Number of patients per treatment arm not reported (quinapril 2.5, 10, 40 mg/day vs. placebo). |
| Canter 1994 [16] | Crossover trial with no pre-crossover data for first 4 weeks of treatment (quinapril 20 mg/day vs. placebo). |
| Cléroux 1994 | Crossover trial with no pre-crossover data for first 4 weeks of |

| Study ID | Reason for exclusion |
|---|---|
| [17] | treatment. 8-week treatment periods but titration in non-responders after 4 weeks treatment (quinapril 10 mg/day vs. placebo). |
| Cuspidi 1997 [18] | Crossover trial with no pre-crossover data for first 4 weeks of treatment (lisinopril 20 mg/day vs. placebo). |
| Duprez 1986 [19] | Crossover trial with no pre-crossover data for first 6 weeks of treatment (enalapril 20 mg/day vs. placebo). |
| Fagard 2001 [20] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (enalapril 20 mg/day vs. losartan 50 mg/day vs. placebo). |
| Gall 1992 [21] | Crossover trial with no pre-crossover data for first 4 weeks of treatment. 8-week treatment periods but titration in non-responders after 4 weeks treatment (captopril 50 mg/day vs. placebo). |
| Gans 1993 [22] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (cilazapril 2.5 mg/day vs. placebo). |
| Gleerup 1996 [23] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (spirapril 6 mg/day vs. placebo). |
| Guitard 1994 [24] | Crossover trial with no pre-crossover data reported for first 3 weeks of treatment (spirapril 3, 6, 12, 24 mg/day vs. placebo). |
| Gupta 1990 [25] Duplicate publication: Gupta 1991 [26] | Crossover trial with no pre-crossover data for first 4 weeks of treatment (quinapril 40 mg/day vs. placebo). |
| Homuth 1993 [27] | Parallel group trial with 6-week treatment period. BP data not extractable from figures (ramipril 2.5, 10, 20 mg/day vs. placebo). |
| Hu 1999 | Parallel group trial with 12-week treatment period, titration in |

| Study ID | Reason for exclusion |
|---|---|
| [28] | non-responders every 4 weeks. Pre-titration data not reported (captopril 50 mg/day vs. placebo). |
| Kahan 1999 [29] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (ramipril 5 mg/day vs. placebo). |
| Karlberg 1997 [30] | Parallel group trial with 4-week treatment period. BP data for placebo group not reported at week 4 (ramipril 5 mg/day vs. ramipril 10 mg/day vs. placebo). |
| Kjeldsen 1992 [31] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (quinapril 40 mg/day vs. placebo). |
| Lacourciere 1999 [32] | Parallel group trial with 8-week treatment period. BP data for placebo group not reported (lisinopril 20 mg/day vs. telmisartan 80 mg/day vs. placebo). |
| Lavezzaro 1990 [33] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (captopril 100 mg/day vs. placebo). |
| Leonetti 1991 [34] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (captopril 50 mg/day vs. placebo). |
| Littler 1990 [35] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (perindopril 8 mg/day vs. placebo). |
| Louis 1992 [36] | Parallel group trial with 4-week treatment period. Only maximum BP reduction is reported (perindopril 2, 4, 8 mg/day vs. placebo). |
| Miyajima 1999 [37] | Parallel group trial with 12-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (imidapril 5 mg/day vs. placebo). |
| Morgan 2001 [38] | Crossover trial with no pre-crossover data for first 4 weeks of treatment. 8-week treatment periods but titration in non-responders after 4 weeks treatment (enalapril 20 mg/day vs. perindopril 4 mg/day vs. placebo). |

| Study ID | Reason for exclusion |
|---|---|
| Petersen 1996 [39] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (spirapril 24 mg/day vs. placebo). |
| Petrie 2000 [40] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (trandolapril 2 mg/day vs. placebo). |
| Petrov 2001 [41] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (enalapril 20 mg/day vs. losartan 50 mg/day vs. placebo). |
| Plouin 1991 [42] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (perindopril 4 mg/day vs. placebo). |
| Pritchard 1996 [43] Duplicate publication: Pritchard 1997 [44] | Crossover trial with no pre-crossover data reported for first 3 weeks of treatment (trandolapril 2 mg/day vs. placebo). |
| Reisin 1997 [45] | Parallel group trial with 12-week treatment period, titration in non-responders every 4 weeks. Pre-titration data not reported (lisinopril 10 mg/day vs. placebo). |
| Salvetti 1987 [46] | Crossover trial with no baseline data and no pre-crossover data reported for first 4 weeks of captopril 100 mg/day vs. placebo. Only mean arterial blood pressure values given. |
| Salvetti 1988 [47] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (captopril 50, 100 mg/day vs. placebo). |
| Salvetti 1989 [48] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (enalapril 10, 20, 40 mg/day vs. placebo). |
| Samuelsson 1992 [49] | Parallel group trial with 8-week treatment period, titration in non-responders at 2 or 4 weeks. Pre-titration data not reported (lisinopril 20 mg/day vs. placebo). |
| Sassano 1984 [50] | Parallel group trial with 6-month treatment period. Additional BP lowering drugs added to enalapril 20 mg in non- |

| Study ID | Reason for exclusion |
|---|---|
| | responders at 4 weeks. Data during first 4 weeks not reported. |
| Scholze 1993 [51] | Parallel group trial with 6-week treatment period. Number of patients per treatment arm not reported (ramipril 2.5, 5, 10 mg/day vs. placebo). |
| Thurig 1995 [52] | Crossover trial with no pre-crossover data reported for first 8 weeks of treatment (lisinopril 20 mg/day vs. placebo). |
| Tomei 1992 [53] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (lisinopril 20 mg/day vs. placebo). |
| Wiggam 1998 [54] | Crossover trial with no pre-crossover data reported for first 8 weeks of treatment (captopril 100 mg/day vs. placebo). |
| Wilkins 1983 [55] | Parallel group trial with 12-week treatment period, titration in non-responders every 4 weeks. Pre-titration data not reported (enalapril 10 mg/day vs. placebo). |
| Wing 1987 [56] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (enalapril 20 mg/day vs. placebo). |
| Wing 1988 [57] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (enalapril 20 mg/day vs. placebo). |
| Youssef 1993 [58] | Parallel group trial with 8-week treatment. Highly suspicious data (enalapril 20 mg/day vs. benazepril 10 mg/day vs. placebo). |
| Zanchetti 2001 [59] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (enalapril 10 mg/day vs. candesartan 4 mg/day vs. placebo). |

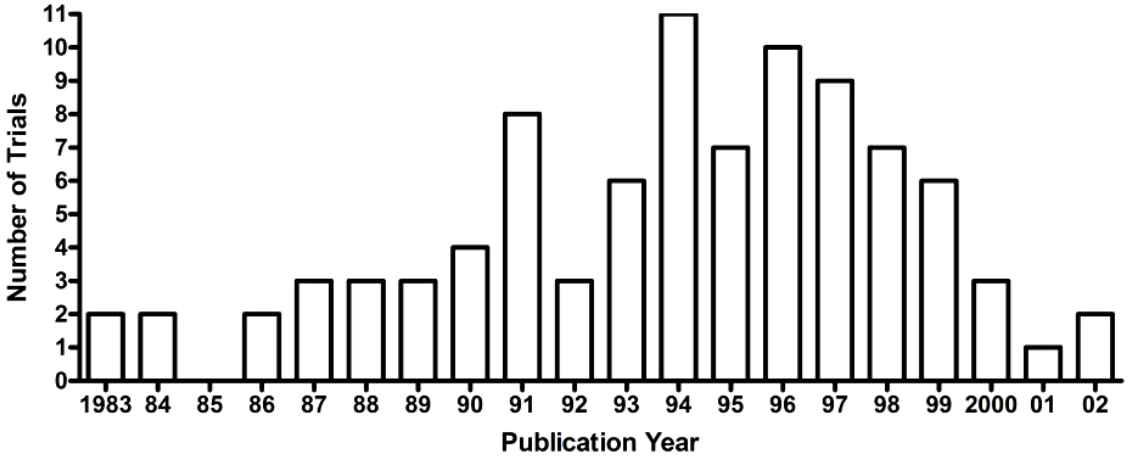
#### 2.2.1.2 Overview of included studies

Of the 92 included studies, 87 (95%) were published in English, 3 (3%) in German, and 2 (2%) in Portuguese. Seventy (76%) of the included studies were industry-sponsored while the remaining 22 (24%) did not report the source of funding. Twenty four duplicate publications of 17 included trials were also identified. Seventy six (82%)

of the included studies randomized patients to fixed-dose monotherapy during double-blind treatment, 8 (9%) were forced-titration studies and 8 (9%) were titration to blood pressure response at pre-specified intervals during the double-blind treatment phase. Only the pre-titration blood pressure data were used in the analysis of these latter 16 studies.

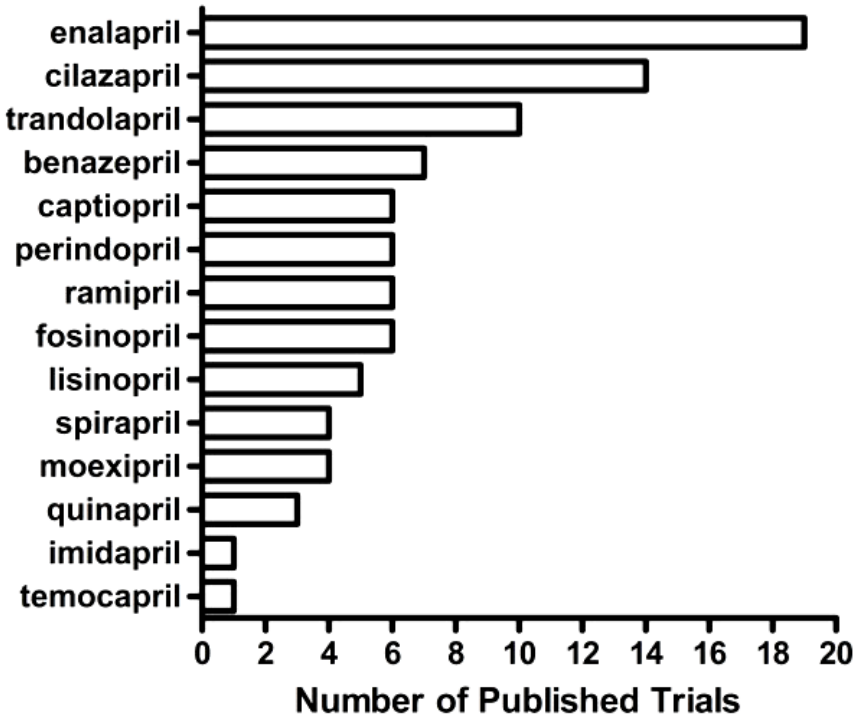
Trials evaluating the antihypertensive efficacy of ACE inhibitor monotherapy using office blood pressure measurements were first published in 1983 (Figure 2.2). There was a steady increase in the number of published studies through the 1980s and early 90s, peaking at 11 trials published in 1994. After 1994, the number of trials published annually steadily declined.

**Figure 2.2: Number of included studies evaluating ACE inhibitors according to publication year**




Enalapril is the most extensively studied ACE inhibitor with 19 published studies investigating the antihypertensive efficacy of daily doses ranging from 5 to 40 mg daily (Figure 2.3).

**Figure 2.3: Number of included studies evaluating ACE inhibitors according to ACE inhibitor studied**




Tables 2.2 - 2.15 summarize the characteristics of each included study. Each study was assigned a unique identifier consisting of the surname of the first author followed by the year of publication.

**Table 2.2: Characteristics of included studies evaluating benazepril**

| Study | Study Description |
|---|---|
| Chrysant 1996 [60]<br>Duplicate publication: Gomez 1991 [61] | **Design:** Placebo run-in period: 1-4 weeks; Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 4<br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg, with a difference of 10 mm Hg or less between visits<br>**Participants:** Benazepril 20 mg: n = 42 (28 males, 14 females); mean age 53.7 years; baseline sitting SBP 153 mm Hg, DBP 104 mm Hg; placebo: n = 40 (22 males, 18 females); mean age 53.5 years; baseline sitting SBP 153 mm Hg, DBP 103 mm Hg<br>**Interventions:** Benazepril 20 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from |

| Study | Study Description |
|---|---|
| | baseline in peak sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Ciba Pharma<br><br>**Notes:** BP change reported and SE of change reported, endpoint BP reported; endpoint SD not reported, SD of change calculated from N and SE of change; BP data from Fagan abstract; SD of change data from Figure 1, p. 8 |
| Kuschnir 1996 [62] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** mean sitting DBP 100-120 mm Hg<br><br>**Participants:** Benazepril 20 mg: n = 77 (32 males, 45 females); mean age 55.8 (8.7) years; baseline sitting SBP 166.8 (14.8) mm Hg, DBP 106.7 (4.6) mm Hg; placebo: n=77 (33 males, 44 females); mean age 57.2 (9.5) years; baseline sitting SBP 166.4 (14.1) mm Hg, DBP 106.9 (4.7) mm Hg<br><br>**Interventions:** Benazepril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported, baseline SBP SD reported, imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Table II, p. 1218 |
| McFate-Smith 1991 [63] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** mean sitting DBP 95-115 mm Hg<br><br>**Participants:** All patients: n = 202; mean age 70 years; baseline sitting SBP 177 mm Hg, DBP 103 mm Hg; benazepril 2 mg: n=50; benazepril 10 mg: n = 50; placebo: n = 50<br><br>**Interventions:** Benazepril 2 mg twice daily; benazepril 10 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in sitting |

| Study | Study Description |
|---|---|
| | SBP/DBP (BP measured 10-14 h post-dose)<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change reported; SD of change not reported, endpoint BP and SD not reported; imputed overall trial mean SD of change; BP data from Table 1, p. IV-81; BP measurement device not reported |
| Moser 1991<br>[64] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** mean sitting DBP 95-114 mm Hg on 2 consecutive visits with ≤ 10 mm Hg difference between 2 visits<br><br>**Participants:** Benazepril 2 mg once daily: n = 34 (24 males, 10 females); mean age 50.4 years; baseline sitting SBP 151.6 (15.9) mm Hg, DBP 102.1 (5.6) mm Hg; benazepril 5 mg once daily: n = 38 (23 males, 15 females); mean age 51.1 years; baseline sitting SBP 152.7 (15.2) mm Hg, DBP 101.2 (5.3) mm Hg; benazepril 10 mg once daily: n = 34 (23 males, 11 females); mean age 51.9 years; baseline sitting SBP 153.1 (13.7) mm Hg, DBP 101.8 (5.7) mm Hg; benazepril 20 mg once daily: n = 36 (23 males, 13 females); mean age 50.4 years; baseline sitting SBP 151.9 (15.7) mm Hg, DBP 101.7 (4.7) mm Hg; placebo: n = 31 (21 males, 10 females); mean age 48.2 years; baseline sitting SBP 150.7 (14.3) mm Hg, DBP 101.7 (4.9) mm Hg<br><br>**Interventions:** Benazepril 2 mg once daily; benazepril 5 mg once daily; benazepril 10 mg once daily; benazepril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SE reported, calculated endpoint SD from N and endpoint SE, imputed endpoint SD for SD of change; DBP data from Table III, p. 325 |
| Pool 2001<br>[65] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 5<br><br>**Inclusion criteria:** mean sitting DBP 100-115 mm Hg<br><br>**Participants:** All patients: n = 454 (286 males, 168 females); mean age 3.8 years; benazepril 10 mg: n = 116; baseline SBP 155.3 mm Hg, DBP 104.2 |

| Study | Study Description |
|---|---|
| | mm Hg, HR 74.2 bpm; placebo: n = 115; baseline SBP 156.1 mm Hg, DBP 105.1 mm Hg, HR 74.4 bpm<br><br>**Interventions:** Benazepril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough sitting HR; WDAE<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** BP change reported, SD of change not reported; endpoint BP and SD not reported, baseline SD not reported, imputed overall trial mean SBP and DBP SD of change; BP and HR data from Table 1, p. 497 |
| Weinberger 1990 [66] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** mean DBP 95-114 mm Hg on 2 consecutive visits with ≤ 10 mm Hg difference between 2 visits<br><br>**Participants:** Benazepril 5 mg: n = 38 (23 males, 15 females); mean age 51.1 years; baseline sitting SBP 152.7 (15.2) mm Hg, DBP 101.2 (5.3) mm Hg; benazepril 10 mg: n = 34 (23 males, 11 females); mean age 51.9 years; baseline sitting SBP 153.1 (13.7) mm Hg, DBP 101.8 (5.7) mm Hg; benazepril 20 mg: n = 36 (23 males, 13 females); mean age 50.4 years; baseline sitting SBP 151.9 (15.7) mm Hg, DBP 101.7 (4.7) mm Hg; benazepril 40 mg: n = 34 (24 males, 10 females); mean age 50.4 years; baseline sitting SBP 151.6 (15.9) mm Hg, DBP 102.1 (5.6) mm Hg; placebo: n = 31 (21 males, 10 females); mean age 48.2 years; baseline sitting SBP 150.7 (14.3) mm Hg, DBP 101.7 (4.9) mm Hg<br><br>**Interventions:** Benazepril 5 mg once daily; benazepril 10 mg once daily; benazepril 20 mg once daily; benazepril 40 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting DBP using mercury sphygmomanometer; mean change from baseline in peak sitting DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change and SE of change reported, endpoint BP reported, endpoint SE not reported; calculated SD of change from N and SE of |

| Study | Study Description |
|---|---|
| | change; DBP data from Table III, p. 325 |
| Whalen 1989<br>[67] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 2<br>**Inclusion criteria:** mean sitting DBP 95-114 mm Hg<br>**Participants:** All patients: n = 165; benazepril 20 mg: n = 50; baseline sitting SBP 156 mm Hg, DBP 103 mm Hg; benazepril 40 mg: n = 50; baseline sitting SBP 154 mm Hg, DBP 102 mm Hg; benazepril 80 mg: n = 37; baseline sitting SBP 161 mm Hg, DBP 104 mm Hg; placebo: n = 50; baseline sitting SBP 154 mm Hg, DBP 103 mm Hg<br>**Interventions:** Benazepril 20 mg once daily; benazepril 40 mg once daily; benazepril 80 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP; mean change from baseline in peak sitting SBP/DBP<br>**Funding source:** Ciba-Geigy Inc.<br>**Notes:** BP change reported; SD of change not reported, endpoint BP and SD not reported; imputed overall trial mean SD of change; BP data from abstract; BP measurement device not reported |

**Table 2.3: Characteristics of included studies evaluating captopril**

| Study | Study Description |
|---|---|
| Drayer 1983<br>[68] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 2<br>**Inclusion criteria:** mean sitting DBP 95-114 mm Hg<br>**Participants:** Captopril 25 mg twice daily: n = 77 (60 males, 17 females); mean age 52 years; baseline supine SBP 156 mm Hg, DBP 101 mm Hg; captopril 50 mg twice daily: n = 71 (50 males, 21 females); mean age 52 years; baseline supine SBP 154 mm Hg, DBP 101 mm Hg; captopril 100 mg twice daily: n = 69 (44 males, 25 females); mean age 55 years; baseline supine SBP 158 mm Hg, DBP 102 mm Hg; placebo: n = 77 (53 males, 24 females); mean age 53 years; baseline supine SBP 157 mm Hg, DBP 102 mm Hg<br>**Interventions:** Captopril 25 mg twice daily; captopril 50 mg twice daily; |

| Study | Study Description |
|---|---|
| | captopril 100 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Percent change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** DBP data from Figure 1, p. III-110; percent change in BP has been converted to absolute BP change data |
| Dupui 1993<br>[69]<br>Duplicate publication:<br>Larrue 1994 [70] | **Design:** Placebo run-in period: Not reported; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean SBP 160-210 mm Hg and DBP 95-115 mm Hg based on 3 separate measurements over a period of several days<br><br>**Participants:** All patients: n = 13 (4 males, 9 females); captopril 75 mg daily: n = 8 (3 males, 5 females); mean age 63 (9) years; baseline upright SBP 155.3 (7.9) mm Hg, DBP 94.4 (10.9) mm Hg; baseline lying SBP 164.3 (10.4) mm Hg, DBP 96.5 (10.7) mm Hg; baseline HR 64.5 (10.7) bpm; placebo: n = 5 (1 male, 4 females); mean age 63 (4) years; baseline upright SBP 157.1 (10.6) mm Hg, DBP 103.0 (16.2) mm Hg; baseline lying SBP 168.1 (7.0) mm Hg, DBP 100.4 (11.1) mm Hg; baseline HR 66.2 (4.9) bpm<br><br>**Interventions:** Captopril 75 mg daily (50 mg in the morning, 25 mg at bedtime); placebo<br><br>**Primary and secondary outcomes:** Upright SBP/DBP using Dinamap automated oscillometric device; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table III, p. 150 |
| Kayanakis 1987<br>[71] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean SBP 160-200 mm Hg and DBP 95-120 mm Hg at 2 consecutive measurements<br><br>**Participants:** Captopril 50 mg: n = 42 (23 males, 19 females); mean age 52.8 (10.6) years; baseline supine SBP 175.5 (8.9) mm Hg, DBP 104.5 (4.4) mm Hg; placebo: n = 83 (47 males, 36 females); mean age 52.8 (9.0) years; |

| Study | Study Description |
|---|---|
| | baseline supine SBP 172.0 (7.7) mm Hg, DBP 102.5 (3.8) mm Hg<br><br>**Interventions:** Captopril 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change for SBP and DBP; SBP data from Figure 1, p. 91S; DBP data from Figure 2, p. 91S |
| Muiesan 1987<br>[72] | **Design:** Placebo run-in period: 3 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 100-110 mm Hg<br><br>**Participants:** All patients: n = 152 (77 males, 75 females); mean age 69 (4) years; captopril 25 mg: n = 52; baseline standing SBP 173 (13) mm Hg, DBP 106 (5) mm Hg; baseline supine SBP 176 (14) mm Hg, DBP 105 (5) mm Hg; placebo: n = 50; baseline standing SBP 172 (14) mm Hg, DBP 106 (5) mm Hg; baseline supine SBP 176 (14) mm Hg, DBP 104 (5) mm Hg<br><br>**Interventions:** Captopril 25 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Standing SBP/DBP using mercury sphygmomanometer; supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Squibb Italia SpA<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change in captopril group; imputed baseline SBP SD for SBP SD of change in placebo group; in placebo group, imputed systematic review overall mean SD of change for DBP; BP data from text and Figure 1, p. S600; baseline supine SBP/DBP and SD for placebo group from Table 1, p. S601 |
| Schoenberger 1986<br>[73] | **Design:** Placebo run-in period: 4-6 weeks; Treatment duration: 8 weeks total, forced titration at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 92-109 mm Hg |

| Study | Study Description |
|---|---|
| | **Participants:** Captopril 50 mg once daily: n = 88 (58 males, 30 females); mean age 52 years; baseline sitting SBP 149.3 mm Hg, DBP 98.2 mm Hg; captopril 50 mg twice daily: n = 91 (60 males, 31 females); mean age 52 years; baseline sitting SBP 151.2 mm Hg, DBP 100.1 mm Hg; placebo: n = 90 (58 males, 32 females); mean age 51 years; baseline sitting SBP 148.7 mm Hg, DBP 98.5 mm Hg<br><br>**Interventions:** Captopril 50 mg once daily; captopril 50 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Sitting DBP<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 BP data only; BP change not reported, SD of change not reported, endpoint SBP not reported; endpoint DBP reported; endpoint SD not reported; baseline SD not reported; imputed overall trial mean SD of change for DBP; DBP data from Table 3, p. 382; BP measurement device not reported |
| VA Study Group 1984 [74]<br>Duplicate publication: VA Study Group 1982 [75] | **Design:** Placebo run-in period: 2-5 weeks; Treatment duration: 7 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 92-109 mm Hg<br><br>**Participants:** Captopril 12.5 mg TID: n = 83 (all males); mean age 55.7 (9.8) years; baseline sitting SBP 147.8 (14.6) mm Hg, DBP 97.0 (3.6) mm Hg; captopril 25 mg TID: n = 84 (all males); mean age 55.7 (8.1) years; baseline sitting SBP 147.4 (11.9) mm Hg, DBP 97.9 (3.7) mm Hg; captopril 37.5 mg BID: n = 88 (all males); mean age 54.9 (7.9) years; baseline sitting SBP 149.0 (13.1) mm Hg, DBP 97.5 (4.7) mm Hg; captopril 50 mg TID: n = 89 (all males); mean age 55.1 (8.0) years; baseline sitting SBP 148.2 (16.0) mm Hg, DBP 98.1 (4.7) mm Hg; placebo: n = 83 (all males); mean age 54.4 (8.0) years; baseline sitting SBP 146.3 (14.6) mm Hg, DBP 97.8 (4.6) mm Hg<br><br>**Interventions:** Captopril 25 mg three times daily; captopril 37.5 mg twice daily; captopril 50 mg three times daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in sitting SBP/DBP using mercury sphygmomanometer (visits were scheduled approx 3 h from the time the patient took his last dose of medication); WDAE |

| Study | Study Description |
|---|---|
| | **Funding source:** E.R Squibb & Sons Inc.<br><br>**Notes:** BP change and SE of change reported; endpoint BP and SD reported; calculated SD of change from N and change SE; BP data from Table 4, p. 1953 |

**Table 2.4: Characteristics of included studies evaluating cilazapril**

| Study | Study Description |
|---|---|
| Boeijinga 1993 [76] | **Design:** Placebo run-in period: Not reported; Treatment duration: 3 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 90-105 mm Hg<br><br>**Participants:** Cilazapril 2.5 mg: n = 14 (11 males, 3 females); mean age 63.7 (4.2) years; baseline SBP 139 mm Hg, DBP 92 mm Hg; placebo: n = 12 (10 males, 2 females); mean age 63.3 (7.8) years; baseline SBP 135 mm Hg, DBP 92 mm Hg<br><br>**Interventions:** Cilazapril 2.5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Peak (2-3 h after dosing) supine SBP/DBP using mercury sphygmomanometer; peak HR; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** Used DBP only since patients did not have SBP $\geq$ 140 mm Hg at baseline; BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from text, p. 446 |
| Carlsen 1995 [77] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg<br><br>**Participants:** Cilazapril 1 mg: n = 42 (26 males, 16 females); mean age 53 years; baseline sitting BP not reported; cilazapril 2.5 mg: n = 42 (28 males, 14 females); mean age 52 years; baseline sitting BP not reported; cilazapril 5 mg: n = 42 (27 males, 15 females); mean age 48 years; baseline sitting BP not reported; placebo: n = 43 (22 males, 21 females); mean age 56 years; baseline sitting BP not reported<br><br>**Interventions:** Cilazapril 1 mg once daily; cilazapril 2.5 mg once daily; |

| Study | Study Description |
|---|---|
| | cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting DBP using mercury sphygmomanometer<br><br>**Funding source:** Roche Ltd.<br><br>**Notes:** SBP change not reported; DBP change and SE of change reported, endpoint DBP and SD not reported; calculated DBP SD of change from N and SE of change; BP data from text, p. 224 |
| Fernandez 1990 [78]<br>Duplicate publication: Fernandez 1990 [79] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 94-114 mm Hg<br><br>**Participants:** Cilazapril 1.25 mg: n = 6 (5 males, 1 female); age 41 (5) years; baseline sitting SBP 133 (7) mm Hg, DBP 97 (3) mm Hg, HR 77 (5) bpm; cilazapril 2.5 mg: n = 6 (5 males, 1 female); age 44 (13) years; baseline sitting SBP 146 (17) mm Hg, DBP 100 (10) mm Hg, HR 77 (13) bpm; cilazapril 5 mg: n = 6 (4 males, 2 females); age 42 (9) years; baseline sitting SBP 144 (8) mm Hg, DBP 98 (4) mm Hg, HR72 (8) bpm; placebo: n = 6 (3 males, 3 females); age 48 (8) years; baseline sitting SBP 150 (10) mm Hg, DBP 101 (3) mm Hg, HR 65 (9) bpm<br><br>**Interventions:** Cilazapril 1.25 mg once daily; cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; trough erect SBP/DBP using mercury sphygmo-manometer; trough supine HR; trough erect HR; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** Only cilazapril 2.5 mg and placebo groups have BP ≥ 140/90 mm Hg after placebo run-in; used supine BP for cilazapril 2.5 mg and placebo groups only; BP change reported and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; data from Table 4, p. 55 |
| Guntzel 1991 [80] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg |

| Study | Study Description |
|---|---|
| | **Participants:** Cilazapril 2.5 mg: n = 29 (17 males, 12 females); mean age 56 (7) years; baseline DBP 103.5 mm Hg; cilazapril 5 mg: n = 29 (22 males, 7 females); mean age 49 (8) years; baseline DBP 103.1 mm Hg; placebo: n = 27 (17 males, 10 females); mean age 52 (9) years; baseline DBP 104.3 mm Hg<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; trough HR; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** Endpoint (week 8) BP change and DBP SE of change reported, endpoint BP and SD reported; BP also reported at weeks 4,6,8; calculated DBP SD of change from N and SE of change; imputed overall trial mean SBP SD of change; BP data from Figure 1, p. 10 |
| Kobrin 1991<br>[81] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg<br><br>**Participants:** Cilazapril 2.5 mg: n = 29 (18 males, 11 females); mean age 50 (9) years; cilazapril 5 mg: n = 29(16 males, 13 females); mean age 48 (9) years; placebo: n = 28 (13 males, 15 females); mean age 52 (8) years<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** Kobrin 1991 reports results for 2 independent RCTs. Study 2 is same RCT as reported in Guntzel 1991. Data for Study 1 is entered as Kobrin 1991; SBP change not reported; DBP change and SE of change reported, endpoint BP and SD not reported; calculated DBP SD of change from N and SE of change; BP data from Table II, p. 34 |
| Krum 1992<br>[82] | **Design:** Placebo run-in period: 3 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2 |

| Study | Study Description |
|---|---|
| | **Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** All patients: n = 22; mean age 59 (11) years; cilazapril 2.5 mg: n = 6; baseline sitting SBP 173 (22) mm Hg, DBP 110 (7.4) mm Hg; placebo: n = 5; baseline sitting SBP 159 (27) mm Hg, DBP 101 (13.4) mm Hg<br><br>**Interventions:** Cilazapril 2.5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using oscillometric device (Dinamap); trough standing SBP/DBP using oscillometric device (Dinamap)<br><br>**Funding source:** Roche Ltd.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SE reported; calculated endpoint SD from N and SE; endpoint SD values are too low; imputed SBP SD of change from baseline SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Table 2, p. 455 |
| Lacourciere 1994 [83] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-109 mm Hg<br><br>**Participants:** All patients: n = 130; 102 (79%) caucasian, 25 (19%) black, 3 (2%) oriental; cilazapril 2.5 mg: n = 44 (22 males, 22 females); mean age 52.5 (9.0) years; baseline sitting SBP 153.6 (16.4) mm Hg, DBP 102.0 (4.7) mm Hg; cilazapril 5 mg: n = 42 (31 males, 11 females); mean age 50.4 (9.1) years; baseline sitting SBP 154.8 (15.1) mm Hg, DBP 101.0 (4.3) mm Hg; placebo: n = 44 (29 males, 15 females); mean age 53.6 (8.5) years; baseline sitting SBP 157.5 (15.8) mm Hg, DBP 101.1 (3.8) mm Hg<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; peak sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported; baseline SBP SD reported, imputed baseline SBP |

| Study | Study Description |
|---|---|
| | SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Table 3, p. 608 |
| Mroczek 1991 [84] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Cilazapril 2.5 mg: n = 59 (45 males, 14 females); mean age 52.4 years; baseline sitting SBP 146.3 mm Hg, DBP 101.1 mm Hg, HR 75.5 bpm; cilazapril 5 mg: n = 59 (41 males, 18 females); mean age 52.9 years; baseline sitting SBP 148.4 mm Hg, DBP 101.3 mm Hg, HR 76.2 bpm; cilazapril 10 mg: n = 58 (34 males, 24 females); mean age 50.3 years; baseline sitting SBP 144.3 mm Hg, DBP 100.8 mm Hg, HR 75.1 bpm; placebo: n = 59 (36 males, 23 females); mean age 54.0 years; baseline sitting SBP 149.8 mm Hg, DBP 100.7 mm Hg, HR 77.3 bpm<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; cilazapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough sitting HR; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SE reported; calculated SD of change from N and SE of change; BP data from text and Table 2, p. 1424 |
| Poirier 1991 [85]<br>Duplicate publication: Lacourciere 1993 [86] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-109 mm Hg, within 10 mm Hg on 2 consecutive weekly visits<br><br>**Participants:** All patients: n = 42 (27 males, 15 females), all white; cilazapril 2.5 mg: n = 14; mean age 53.6 (8.0) years; baseline sitting SBP 153.6 (16.4) mm Hg, DBP 102.0 (4.7) mm Hg; cilazapril 5 mg: n = 14; mean age 53.1 (8.2) years; baseline sitting SBP 154.8 (15.1) mm Hg, DBP 101.0 (4.3) mm Hg; placebo: n = 14; mean age 55.1 (7.7) years; baseline sitting SBP 157.5 (15.8) mm Hg, DBP 101.1 (3.8) mm Hg |

| Study | Study Description |
|---|---|
| | **Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported; baseline SBP SD reported, imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Table 1, p. 914 |
| Pordy 1994<br>[87] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Cilazapril 0.5-10 mg: n = 288 (166 males, 122 females); mean age 53.9 (12.1) years; baseline sitting DBP 100.4 mm Hg; placebo: n = 97 (57 males, 40 females); mean age 53.0 (11.9) years; baseline sitting DBP 100.3 mm Hg<br><br>**Interventions:** Cilazapril 0.5 mg once daily; cilazapril 5 mg once daily; cilazapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** SBP not reported; DBP change and SD of change reported, endpoint BP and SD not reported; BP data from Table 3, p. 315 |
| Prager 1994<br>[88] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Cilazapril 2.5 mg: n = 54 (36 males, 18 females); mean age 55.6 (10.1) years; baseline sitting SBP 162.5 (15.1) mm Hg, DBP 102.4 (5.4) mm Hg; cilazapril 5 mg: n = 55 (32 males, 23 females); mean age 55.6 (10.8) years; baseline sitting SBP 158.8 (16.5) mm Hg, DBP 100.8 (4.3) mm Hg; placebo: n = 53 (29 males, 24 females); mean age 58.1 (9.5) years; |

| Study | Study Description |
|---|---|
| | baseline sitting SBP 161.4 (16.5) mm Hg, DBP 102.1 (5.7) mm Hg<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 2, p. S95 |
| Uusitupa 1996 [89] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg and mean daytime ambulatory DBP 90-105 mm Hg<br><br>**Participants:** Cilazapril 2.5 mg: n = 19 (10 males, 9 females); mean age 53.7 (5.7) years; baseline sitting SBP 157.3 (17.1) mm Hg, DBP 104.0 (8.0) mm Hg, HR 70 (13) bpm; placebo: n = 20 (14 males, 6 females); mean age 50.5 (9.5) years; baseline sitting SBP 147.0 (10.3) mm Hg, DBP 99.4 (5.3) mm Hg, HR 70 (10) bpm<br><br>**Interventions:** Cilazapril 2.5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** BP change reported; SD of change not reported; 95% confidence interval of change reported; calculated SD of change from 95% CI of change; endpoint BP and SD reported; BP change data from Table 6, p. 323; endpoint BP data from Table 4, p. 322 |

| Study | Study Description |
|---|---|
| White 1988<br>[90] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 12 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean DBP 95-114 mm Hg<br><br>**Participants:** All patients: n = 18 (10 males, 8 females); mean age 52 (12) years; cilazapril 2.5 mg: n = 9; baseline sitting SBP 155 (15) mm Hg, DBP 104 (4) mm Hg, HR 77 (8) bpm; placebo: n = 9; baseline sitting SBP 152 (15) mm Hg, DBP 100 (4) mm Hg, HR 83 (8) bpm<br><br>**Interventions:** Cilazapril 2.5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; trough standing SBP/DBP using mercury sphygmo-manometer; trough sitting HR; trough standing HR; WDAE<br><br>**Funding source:** Hoffman-La Roche Ltd.<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 1, p. 174 |
| Yodfat 1993<br>[91] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP > 100 mm Hg<br><br>**Participants:** Cilazapril: n = 94 (67 males, 27 females); mean age 52.4 (8.1) years; baseline BP not reported; placebo: n = 46 (28 males, 18 females); mean age 54.1 (7.0) years; baseline BP not reported<br><br>**Interventions:** Cilazapril 2.5 mg once daily; cilazapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** SBP change not reported; DBP change reported; SD of change not reported, endpoint SBP/DBP and SD not reported; imputed overall trial mean SD of change for DBP; baseline BP not reported; BP data from Figure 1, p. 119 |

**Table 2.5: Characteristics of included studies evaluating enalapril**

| Study | Study Description |
|---|---|
| Applegate 1996 [92] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Enalapril 5 mg: n = 56 (38 males, 18 females); mean age 52.5 (11.2) years; baseline SBP 152.8 (17.3) mm Hg, DBP 100.5 (5.2) mm Hg, HR 77.4 (9.2) bpm; placebo: n = 58 (39 males, 19 females); mean age 54.2 (10.2) years; baseline SBP 152.5 (13.0) mm Hg, DBP 100.4 (4.8) mm Hg, HR 76.8 (10.0) bpm<br><br>**Interventions:** Enalapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in SBP/DBP using mercury sphygmomanometer; trough sitting SBP/DBP using mercury sphygmomanometer; HR; WDAE<br><br>**Funding source:** Merck<br><br>**Notes:** Adjusted BP change reported, SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; used endpoint BP and SD data to calculate change in BP instead of entering adjusted BP change data; BP data from Table II, p. 53 |
| Cushman 1998 [93] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg, with a difference of 7 mm Hg or less between these means; mean sitting SBP had to be < 210 mm Hg<br><br>**Participants:** Enalapril 5 mg: n = 144 (94 males, 50 females); mean age 56.1 (10.0) years; baseline sitting SBP 155.2 mm Hg, DBP 101.6 (5.5) mm Hg; placebo: n = 150 (104 males, 46 females); mean age 55.8 (11.4) years; baseline sitting SBP 155.4 mm Hg, DBP 101.6 (5.6) mm Hg<br><br>**Interventions:** Enalapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Merck |

| Study | Study Description |
|---|---|
| | **Notes:** BP change and SD of change not reported; endpoint BP reported; endpoint SD not reported; imputed overall trial mean SD of change for SBP and DBP; BP data from Table 2, p. 26 |
| Gerritsen 1998 [94] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 90-115 mm Hg and SBP ≤ 200 mm Hg<br><br>**Participants:** Enalapril 10 mg: n = 40 (28 males, 12 females); mean age 58.8 (9.5) years; baseline SBP 165 (15) mm Hg, DBP 92 (7.8) mm Hg, HR 81.2 (13.3) bpm; placebo: n = 41 (26 males, 15 females); mean age 61.9 (7.8) years; baseline SBP 166 (18) mm Hg, DBP 93 (8.2) mm Hg, HR 81.2 (14.3) bpm<br><br>**Interventions:** Enalapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough SBP/DBP using automated device (Dinamap); WDAE<br><br>**Funding source:** Bayer<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD for SD of change; position of BP measurement not reported but likely sitting; BP data from Figure 1, p. 693 |
| Gradman 1995 [95] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 100-115 mm Hg at weeks 2 and 4 of run-in, with a difference of 7 mm Hg or less between these means<br><br>**Participants:** Enalapril 20 mg: n = 83 (56 males, 27 females); median age 53 years; baseline SBP 155.4 mm Hg, DBP 103.1 mm Hg; placebo: n = 78 (47 males, 31 females); median age 53 years; baseline SBP 157.9 mm Hg, DBP 103.3 mm Hg<br><br>**Interventions:** Enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP; mean change from baseline in peak supine SBP/DBP; |

| Study | Study Description |
|---|---|
| | WDAE<br><br>**Funding source:** Merck<br><br>**Notes:** BP change and SD of change reported, endpoint BP reported; endpoint SD not reported, BP data from Table 2, p. 1348; BP measurement device not reported |
| Gradman 1997<br>[96] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** All patients: n = 707 (457 males, 250 females); mean age 53.5 (10.5) years; baseline sitting SBP 155.5 (17.7) mm Hg, DBP 101.9 (5.7) mm Hg; enalapril 5 mg: n = 85; enalapril 20 mg: n = 48; placebo: n = 79<br><br>**Interventions:** Enalapril 5 mg once daily; enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Astra Merck Inc.<br><br>**Notes:** BP change reported; SD of change not reported; endpoint BP and SD not reported; baseline SBP SD for all groups reported; imputed baseline SBP SD for SD of change; imputed systematic review overall mean SD of change for DBP; DBP data from Figure 1, p. 432; SBP data from Figure 2, p. 433 |
| Guitard 1997<br>[97] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean DBP 100-115 mm Hg<br><br>**Participants:** Enalapril 5 mg: n = 101 (54 males ,47 females); mean age 56.2 (9.7) years; baseline SBP 163.2 (16.4) mm Hg, DBP 99.5 (6.1) mm Hg; spirapril 6 mg: n = 101 (50 males, 50 females); mean age 58.0 (7.9) years; baseline SBP 161.8 (16.3) mm Hg, DBP 99.7 (6.6) mm Hg; placebo: n = 50 (32 males, 18 females); mean age 56.5 (8.2) years; baseline SBP 161.3 (18.2) mm Hg, DBP 98.2 (6.9) mm Hg<br><br>**Interventions:** Enalapril 5 mg once daily; spirapril 6 mg once daily; placebo |

| Study | Study Description |
|---|---|
| | **Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting DBP; adjusted mean change from baseline in peak sitting DBP<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Used week 4 BP data only; BP change reported, SD of change not reported, endpoint BP reported, endpoint SD not reported; imputed overall trial mean DBP SD of change; DBP data from Table 5, p. 455; BP measurement device not reported |
| Holwerda 1996 [98] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Enalapril 20 mg: n = 69 (40 males, 29 females); mean age 52.5 (10.3) years; baseline sitting SBP 161.5 (10.4) mm Hg, DBP 102.2 (4.2) mm Hg; valsartan 80 mg: n = 137 (65 males, 72 females); mean age 53.1 (12.4) years; baseline sitting SBP 161.7 (11.6) mm Hg, DBP 101.2 (4.5) mm Hg; placebo: n = 142 (76 males, 66 females); mean age 53.1 (12.9) years; baseline sitting SBP 161.0 (11.5) mm Hg, DBP 101.8 (4.4) mm Hg<br><br>**Interventions:** Enalapril 20 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 3, p. 1150 |
| Krum 1998 [99] | **Design:** Placebo run-in period: 4-6 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg, DBP could not differ by more than 7 mm Hg on 3 consecutive visits<br><br>**Participants:** Enalapril 20 mg: n = 50 (33 males, 17 females); mean age 59 (10) years; baseline SBP 161.9 (14.3) mm Hg, DBP 102.2 (5.0) mm Hg, HR 76.2 (8.4) bpm; placebo: n = 49 (27 males, 22 females); mean age 56 (9) years; baseline SBP 158.3 (14.1) mm Hg, DBP 101.7 (4.5) mm Hg, HR 71.8 |

| Study | Study Description |
|---|---|
| | (7.8) bpm<br><br>**Interventions:** Enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough sitting HR; WDAE<br><br>**Funding source:** Hoffman-La Roche<br><br>**Notes:** BP change and SD of change reported; endpoint BP and SD not reported; SBP/DBP data from Table 2, p. 788 |
| Kuppers 1997<br>[100] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Enalapril 10 mg once daily: n = 77 (32 males, 45 females); mean age 55.8 (8.7) years; baseline sitting SBP 166.8 (14.8) mm Hg, DBP 106.7 (4.6) mm Hg; placebo: n = 77 (33 males, 44 females); mean age 57.2 (9.5) years; baseline sitting SBP 166.4 (14.1) mm Hg, DBP 106.9 (4.7) mm Hg<br><br>**Interventions:** Enalapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Solvay Pharma<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Figure 1, p. 95 |
| Levine 1995<br>[101] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 12 weeks total, forced titration every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP ≥ 95 mm Hg<br><br>**Participants:** Enalapril 10 mg: n = 31 (17 males, 14 females); mean age 56 years; baseline SBP 152.5 (13.4) mm Hg, DBP 102.5 (5.0) mm Hg; placebo: n = 29 (17 males, 12 females); mean age 53 years; baseline SBP 149.8 (14.5) mm Hg, DBP 100.2 (4.3) mm Hg |

| Study | Study Description |
|---|---|
| | **Interventions:** Enalapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Lederle Laboratories<br><br>**Notes:** Used week 4 BP data only; BP change and SE of change reported, endpoint BP and endpoint SE reported, calculated SD of change from N and SE of change; SBP data from Table 2, p. 496; DBP data from Table 3, p. 497 |
| Oparil 1999<br>[102] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg and difference between their average sitting DBP values for last 2 visits of placebo run-in period did not exceed 12 mm Hg<br><br>**Participants:** Enalapril 20 mg: n = 45 (23 males, 22 females); baseline sitting SBP 154.6 (14.1) mm Hg, DBP 100.9 (4.7) mm Hg, HR 74.8 (9.4) bpm; eprosartan: n = 46 (27 males, 19 females); baseline sitting SBP 153.1 (14.9) mm Hg, DBP 101.5 (4.1) mm Hg, HR 75.9 (7.5) bpm; placebo: n = 45 (21 males, 24 females); baseline sitting SBP 154.1 (14.1) mm Hg, DBP 99.8 (4.0) mm Hg, HR 74.4 (8.1) bpm<br><br>**Interventions:** Enalapril 20 mg once daily; eprosartan 300 mg twice (200 mg for first 3 days) daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in sitting DBP; WDAE<br><br>**Funding source:** SmithKline Beecham Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported, DBP data from text, p. 8 and Figure 3, p. 10; time of BP measurement not reported; BP measurement device not reported |
| Prichard 2002<br>[103] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg and sitting SBP $\leq$ 200mm Hg during 2 weeks immediately prior to randomization<br><br>**Participants:** Enalapril 20 mg once daily: n = 53 (35 males, 18 females); mean age 52.2 (10.3) years; baseline sitting SBP 165.2 (14.5) mm Hg, DBP |

| Study | Study Description |
|---|---|
| | 101.1 (4.4) mm Hg; baseline HR 78.0 (7.3) bpm; placebo: n = 50 (29 males, 21 females); mean age 53.7 (8.7) years; baseline sitting SBP 162.8 (14.5) mm Hg, DBP 99.9 (3.9) mm Hg; baseline HR 76.6(8.8) bpm<br><br>**Interventions:** Enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Solvay Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD reported, BP data from Table II, p. 169 |
| Roca-Cusachs 2001 [104] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean DBP 90-109 mm Hg, which differed by < 10 mm Hg from that observed in previous run-in visit<br><br>**Participants:** All patients (per protocol population): n = 342 (137 males, 205 females); mean age 55.6 (9.9) years; baseline sitting SBP 158.3 (10.6) mm Hg, DBP 98.6 (5.3) mm Hg<br><br>**Interventions:** Enalapril 5 mg once daily; enalapril 10 mg once daily; enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** VITA INVEST<br><br>**Notes:** BP change and SD of change not reported, endpoint BP reported; endpoint SD not reported; baseline SD reported; imputed baseline SBP SD for SD of change; imputed overall trial mean DBP SD of change; BP data from Figure 1, p. 844 |
| Simon 1983 [105]<br>Duplicate publication: Morioka 1983 [106] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks total, forced titration every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Not reported but baseline DBP for all groups is at least 90 mm Hg<br><br>**Participants:** All patients: n = 34 (33 male, 1 female) white patients; |

| Study | Study Description |
|---|---|
| | enalapril once and twice daily: n = 21; mean age 52 (11) years; baseline SBP 143 (15) mm Hg, DBP 93 (5) mm Hg; placebo: n = 12; mean age 50 (17) years; baseline SBP 150 (14) mm Hg, DBP 92 (7) mm Hg<br><br>**Interventions:** Enalapril 10 mg once daily; enalapril 10 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 DBP only since patients treated with enalapril 10 mg once daily did not have SBP ≥ 140mm Hg at baseline; BP change and SD of change not reported; endpoint BP reported; endpoint SD not reported; imputed overall trial mean SD of change; BP data from Figure 1, p. 461; BP measurement device not reported |
| Smith 1998<br>[107] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br><br>**Participants:** Enalapril 20 mg: n = 72 (44 males, 28 females); mean age 53.1 (11.0) years; baseline supine SBP 153.8 (13.8) mm Hg, DBP 100.4 (4.2) mm Hg; placebo: n = 76 (49 males, 27 females); mean age 55.6 (9.6) years; baseline supine SBP 154.8 (11.8) mm Hg, DBP 100.4 (4.5) mm Hg<br><br>**Interventions:** Enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Boehringer Ingelheim Pharma<br><br>**Notes:** BP change and SE of change reported; endpoint BP and SD not reported; calculated SD of change from N and SE of change; change in BP data from Figures 1 and 2, p. 235; SE of change data from Table 2, p. 234 |
| Smith 2000<br>[108] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 100-114 mm Hg during final 2 weeks of run-in, mean supine DBP could not vary by more than 7 mm Hg between weeks 2 and 3 or weeks 3 and 4 of run-in, or by more than 10 mm Hg |

| Study | Study Description |
|---|---|
| | between weeks 2 and 4 of run-in<br><br>**Participants:** Enalapril 20 mg: n = 42 (31 males, 11 females); mean age 52.0 years; baseline supine SBP 155.3 mm Hg, DBP 103.3 mm Hg, HR 72.7 bpm; placebo: n = 43 (24 males, 19 females); mean age 52.0 years; baseline supine SBP 159.5 mm Hg, DBP 104.9 mm Hg, HR 72.5 bpm<br><br>**Interventions:** Enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough standing HR; mean change from baseline in trough supine HR; WDAE<br><br>**Funding source:** Boehringer Ingelheim Pharma<br><br>**Notes:** BP change and SE of change reported; endpoint BP and SD not reported; calculated SD of change from N and SE of change; change in BP data from Table II, p. 1385 |
| Waeber 1999<br>[109] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg<br><br>**Participants:** Enalapril 10 mg: n = 321 (188 males, 133 females); mean age 52.4 (10.2) years; baseline sitting SBP 158.0 (15.4) mm Hg, DBP 100.9 (4.6) mm Hg; placebo: n = 304 (165 males, 135 females); mean age 51.0 (10.7) years; baseline SBP 157.2 (15.3) mm Hg, DBP 101.0 (4.4) mm Hg<br><br>**Interventions:** Enalapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change reported, endpoint BP and SD not reported; BP data from Figure I, p. 917 |
| Whelton 1992<br>[110] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3 |

| Study | Study Description |
|---|---|
| | **Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Enalapril 10 mg: n = 36 (24 males, 12 females); mean age 53 years; baseline sitting SBP 152.9 mm Hg, DBP 100.5 mm Hg; lisinopril 10 mg: n = 37 (22 males, 15 females); mean age 51 years; baseline sitting SBP 146.9 mm Hg, DBP 99.1 mm Hg; placebo: n = 37 (23 males, 14 females); mean age 50 years; baseline sitting SBP 149.9 mm Hg, DBP 99.5 mm Hg<br><br>**Interventions:** Enalapril 10 mg once daily; lisinopril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Baseline adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** ICI Americas Inc.<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; calculated SD of change from N and change SE; BP data from Table II, p. 328 |
| White 2002<br>[111] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 8 weeks total, forced titration at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg during 2 consecutive weeks; also required that ambulatory awake DBP ≥ 85 mm Hg<br><br>**Participants:** Enalapril 10 mg: n = 99 (58 males, 41 females); mean age 54 (10) years; baseline SBP 145 (16) mm Hg, DBP 93 (8) mm Hg; baseline HR 72 (10) bpm; placebo: n = 46 (30 males, 16 females); mean age 56 (11) years; baseline SBP 148 (12) mm Hg, DBP 95 (6) mm Hg; baseline HR 71 (9) bpm<br><br>**Interventions:** Enalapril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change reported, endpoint BP and SD not reported; BP data from Table IV, p. 663 |

**Table 2.6: Characteristics of included studies evaluating fosinopril**

| Study | Study Description |
|---|---|
| Fernandez 1994 [112] | **Design:** Placebo run-in period: 4-5 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg at 2 consecutive visits 1 week apart<br><br>**Participants:** Fosinopril 20 mg: n = 16 (7 males, 9 females); mean age 48.8 (11.6) years; baseline sitting SBP 149.7 (12.0) mm Hg, DBP 101.9 (4.4) mm Hg, HR 72.9 bpm; placebo: n = 17 (2 males, 15 females); mean age 53.2 (7.0) years; baseline sitting SBP 146.6 (9.9) mm Hg, DBP 100.3 (3.7) mm Hg, HR 73.4 bpm<br><br>**Interventions:** Fosinopril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SD of change reported; endpoint BP and SD not reported; BP data from Table 2, p. I-209 |
| Ford 1993 [113] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-115 mm Hg<br><br>**Participants:** Fosinopril 10 mg: n = 17 (4 males, 13 females); mean age 49 (9.1) years; baseline supine SBP 163.8 mm Hg, DBP 102.2 mm Hg; baseline HR 77.4 bpm; fosinopril 20 mg: n = 15 (6 males, 9 females); mean age 55 (8.1) years; baseline supine SBP 161.2 mm Hg, DBP 100.2 mm Hg; baseline HR 73.9 bpm; fosinopril 40 mg: n = 16 (9 males, 7 females); mean age 51 (9.6) years; baseline supine SBP 164.4 mm Hg, DBP 101.8 mm Hg; baseline HR 77.8 bpm; placebo: n = 16 (0 males, 16 females); mean age 56 (14) years; baseline supine SBP 154.7 mm Hg, DBP 99.8 mm Hg; baseline HR 74.2 bpm<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; trough HR; WDAE<br><br>**Funding source:** Bristol-Myers Squibb |

| Study | Study Description |
|---|---|
| | **Notes:** BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported; imputed overall trial mean SBP and DBP SD of change; BP data from Table II, p. 327; trough and peak BP data also available in Figures 1 and 2, p.327 |
| Pizarro 1996 [114] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-110 mm Hg<br><br>**Participants:** Fosinopril 20 mg: n = 16 (4 males, 12 females); mean age 56.4 (8.1) years; baseline sitting SBP 151.8 (14.0) mm Hg, DBP 100.8 (4.8) mm Hg, HR 75.9 (11.9) bpm; placebo: n = 18 (2 males, 15 females); mean age 53.2 (7.0) years; baseline sitting SBP 160.1 (22.1) mm Hg, DBP 100.1 (2.4) mm Hg, HR 72.3 (6.1) bpm<br><br>**Interventions:** Fosinopril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP; trough HR; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** SBP change not reported, DBP change reported; SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from text, p. 496 and p. 460; BP measurement device not reported |
| Pool 1990 [115] | **Design:** Placebo run-in period: 4-6 weeks. Treatment duration: 12 weeks total, titration-to-response every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg on 2 consecutive visits<br><br>**Participants:** All patients: n = 418 patients randomized to double-blind treatment; n = 380 who completed 4 weeks of double-blind treatment included in efficacy analysis; fosinopril 5 mg: n = 83 randomized; for efficacy analysis n = 74 (53 males, 21 females); mean age 53.2 years; baseline sitting SBP 151.7 mm Hg, DBP 101.4 mm Hg; fosinopril 10 mg: n = 84 randomized; for efficacy analysis n = 71 (55 males, 16 females); mean age 53.5 years; baseline sitting SBP 148.6 mm Hg, DBP 100.9 mm Hg; fosinopril 20 mg: n = 84 randomized; for efficacy analysis n = 79 (51 males, 28 females); mean age 54.2 years; baseline sitting SBP 153.2 mm Hg, DBP |

| Study | Study Description |
|---|---|
| | 102.4 mm Hg; fosinopril 40 mg: n = 85 randomized; for efficacy analysis n = 79 (52 males, 27 females); mean age 50.9 years; baseline sitting SBP 153.0 mm Hg, DBP 102.2 mm Hg; placebo: n = 82 randomized; for efficacy analysis n = 77 (52 males, 25 females); mean age 53.2 years; baseline sitting SBP 151.7 mm Hg, DBP 101.4 mm Hg<br><br>**Interventions:** Fosinopril 5 mg once daily; fosinopril 10 mg once daily; fosinopril 20 mg once daily; fosinopril 40 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change in trough sitting SBP/DBP using mercury sphygmomanometer; mean change in trough standing SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported; baseline SD not reported; imputed overall trial mean SD of change for SBP and DBP; change in SBP data from Figure 2, p. 524; change in DBP data from Table II, p. 526 |
| Pool 1997<br>[116] | **Design:** Placebo run-in period: 4-5 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg<br><br>**Participants:** All patients: n = 548 (335 males, 213 females); mean age 51.5 (11.0) years; baseline sitting SBP 149.5 (15.7) mm Hg, DBP 100.1 (4.0) mm Hg; fosinopril 2.5 mg: n = 33 randomized; BP data reported for n = 29; baseline sitting SBP 153.0 mm Hg, DBP 100.4 mm Hg; fosinopril 10 mg: n = 30 randomized; BP data reported for n = 29; baseline sitting SBP 147.4 mm Hg, DBP 99.6 mm Hg; fosinopril 40 mg: n = 32 randomized; BP data reported for n = 28; baseline sitting SBP 147.2 mm Hg, DBP 98.6 mm Hg; placebo: n = 32 randomized; BP data reported for n = 29; baseline sitting SBP 150.4 mm Hg, DBP 99.8 mm Hg<br><br>**Interventions:** Fosinopril 2.5 mg once daily; fosinopril 10 mg once daily; fosinopril 40 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; trough sitting SBP/DBP using mercury sphygmomanometer; WDAE |

| Study | Study Description |
|---|---|
| | **Funding source:** Bristol-Myers Squibb<br><br>**Notes:** Adjusted BP change reported, SD of change not reported, endpoint BP reported; endpoint SD not reported; baseline SD not reported; imputed overall trial mean SD of change for SBP and DBP; used endpoint BP data to calculated change in BP instead of entering adjusted BP change data; BP data from Tables 3 and 4, p. 120 |
| Zamboulis 1996 [117] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Fosinopril 20 mg: n = 12 (8 males, 4 females); mean age 51 years; baseline sitting SBP 150.8 (15.9) mm Hg, DBP 108.8 (4.7) mm Hg; baseline HR 76.9 (5.3) bpm; placebo: n = 11 (7 males, 4 females); mean age 45 years; baseline sitting SBP 143.0 (20.0) mm Hg, DBP 95.5 (12.6) mm Hg; baseline HR 79.0 (9.8) bpm<br><br>**Interventions:** Fosinopril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 1, p. 254; time of BP measurement (peak and/or trough) not reported |

**Table 2.7: Characteristics of included studies evaluating imidapril**

| Study | Study Description |
|---|---|
| Vandenburg 1994 [118] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Imidapril 5 mg: n = 33 (21 males, 12 females); mean age 53.2 (12.1) years; baseline sitting DBP 102.3 (5.7) mm Hg; imidapril 10 mg: n = 31 (18 males, 13 females); mean age 52.3 (11.7) years; baseline sitting DBP 100.8 (4.5) mm Hg; imidapril 20 mg: n = 31 (16 males, 15 females); mean age 52.5 (10.0) years; baseline sitting DBP 101.0 (5.6) mm Hg; imidapril 40 |

| Study | Study Description |
|---|---|
| | mg: n = 32 (21 males, 11 females); mean age 49.8 (13.6) years; baseline sitting DBP 102.2 (5.1) mm Hg; placebo: n = 35 (20 males, 15 females); mean age 51.9 (11.8) years; baseline sitting DBP 101.3 (5.3) mm Hg<br><br>**Interventions:** Imidapril 5 mg once daily; imidapril 10 mg once daily; imidapril 20 mg once daily; imidapril 40 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; trough standing SBP/DBP using mercury sphygmo-manometer; WDAE<br><br>**Funding source:** Tanabe Pharma<br><br>**Notes:** BP change and SD of change reported; endpoint BP and SD reported; change in BP data from Table 4, p. 271 |

**Table 2.8: Characteristics of included studies evaluating lisinopril**

| Study | Study Description |
|---|---|
| Black 1997<br><br>[119] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 12 weeks total, titration-to-response every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Lisinopril 10 mg: n = 187 (112 males, 75 females); mean age 53.9 (10.7) years; baseline sitting SBP 153.9 (14.9) mm Hg, DBP 101.0 (4.5) mm Hg; placebo: n = 183 (113 males, 70 females); mean age 54.0 (11.8) years; baseline sitting SBP 154.1 (14.4) mm Hg, DBP 101.0 (4.4) mm Hg<br><br>**Interventions:** Lisinopril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Least mean square change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** Used week 4 BP data only; BP change reported, SD of change not reported, endpoint BP and SD not reported; imputed SBP SD of change from baseline SBP SD of change, imputed overall trial mean DBP SD of change; SBP data from Figure 1, p. 487, DBP data from text, p. 485 |
| Chan 1997 | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks |

| Study | Study Description |
|---|---|
| [120] | **Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg at last 2 visits of run-in<br><br>**Participants:** Lisinopril 10 mg: n = 26 (18 males, 8 females); mean age 70.5 years; baseline sitting SBP 163.8 (13.0) mm Hg, DBP 104.9 (5.0) mm Hg, HR 62.5 bpm; placebo: n = 27 (15 males, 12 females); mean age 73.4 years; baseline sitting SBP 167.9 (14.8) mm Hg, DBP 105.5 (5.4) mm Hg, HR 61.9 bpm<br><br>**Interventions:** Lisinopril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD reported; SD of change values are too low; imputed endpoint SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; SBP data from Table 2, p. 745; DBP data from Table 3, p. 746 |
| Chrysant 1994<br>[121] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 100-114 mm Hg<br><br>**Participants:** Lisinopril 10 mg: n = 85; mean age 54 years; baseline sitting SBP 154 mm Hg, DBP 104 mm Hg, HR 77 bpm; baseline upright SBP 154 mm Hg, DBP 103 mm Hg, HR 78 bpm; placebo: n = 81; mean age 53 years; baseline sitting SBP 155 mm Hg, DBP 103 mm Hg, HR 77 bpm; baseline upright SBP 154 mm Hg, DBP 104 mm Hg, HR 79 bpm<br><br>**Interventions:** Lisinopril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; trough upright SBP/DBP using mercury sphygmo-manometer<br><br>**Funding source:** ICI Pharma<br><br>**Notes:** BP change and SD of change not reported, endpoint BP reported and SEM reported; calculated endpoint SD from N and endpoint SEM; imputed endpoint SD for SD of change; BP data from Figure 1, p. 739 |

| Study | Study Description |
|---|---|
| Gomez 1989<br>[122] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine DBP 95-115 mm Hg<br>**Participants:** Lisinopril 1.25 mg: n = 41 (38 males, 3 females); mean age 58 years; baseline BP not reported for all randomized patients; lisinopril 5 mg: n = 41 (37 males, 4 females); mean age 56 years; baseline BP not reported for all randomized patients; lisinopril 20 mg: n = 44 (42 males, 2 females); mean age 54 years; baseline BP not reported for all randomized patients; lisinopril 80 mg: n = 43 (37 males, 6 females); mean age 57 years; baseline BP not reported for all randomized patients; placebo: n = 47 (40 males, 7 females); mean age 56 years; baseline BP not reported for all randomized patients<br>**Interventions:** Lisinopril 1.25 mg once daily; lisinopril 5 mg once daily; lisinopril 20 mg once daily; lisinopril 80 mg once daily (patients received 40 mg once daily for the first 2 weeks and then 80 mg once daily for the last 4 weeks); placebo<br>**Primary and secondary outcomes:** Trough erect SBP/DBP using mercury sphygmomanometer; trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br>**Funding source:** Merck Sharp & Dohme<br>**Notes:** BP change and 95% CI reported, endpoint BP reported, endpoint SD not reported; calculated SD of change from 95% CI; erect BP data from Table 3, p. 418; supine BP data from Table 2, p. 417 |
| Whelton 1992<br>[110] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br>**Participants:** Lisinopril 10 mg: n = 37 (22 males, 15 females); mean age 51 years; baseline sitting SBP 146.9 mm Hg, DBP 99.1 mm Hg; enalapril 10 mg: n = 36 (24 males, 12 females); mean age 53 years; baseline sitting SBP 152.9 mm Hg, DBP 100.5 mm Hg; placebo: n = 37 (23 males, 14 females); mean age 50 years; baseline sitting SBP 149.9 mm Hg, DBP 99.5 mm Hg<br>**Interventions:** lisinopril 10 mg once daily; enalapril 10 mg once daily; placebo |

| Study | Study Description |
|---|---|
| | **Primary and secondary outcomes:** Baseline adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** ICI Americas Inc.<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; calculated SD of change from N and change SE; BP data from Table II, p. 328 |

**Table 2.9: Characteristics of included studies evaluating moexipril**

| Study | Study Description |
|---|---|
| Koch 1999<br><br>[123] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Moexipril 15 mg: n = 47; mean age 56.1 (8.0) years; baseline sitting SBP 154.6 (11.8) mm Hg, DBP 99.5 (3.8) mm Hg, HR 72.7 (7.7) bpm; placebo: n = 48; mean age 57.0 (6.8) years; baseline sitting SBP 158.5 (13.6) mm Hg, DBP 100.0 (3.7) mm Hg, HR 72.4 (6.3) bpm<br><br>**Interventions:** Moexipril 15 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Schwarz Pharma<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported; baseline SD reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean SD of change for DBP; change in BP data from text and Figure 1, p. 339 |
| Mroczek 1996<br><br>[124] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg at last 2 consecutive visits<br><br>**Participants:** Moexipril 7.5 mg: n = 51 (31 males, 20 females); mean age 54.9 years; baseline sitting SBP 152.2 mm Hg, DBP 101.8 mm Hg, HR 75.8 |

| Study | Study Description |
|---|---|
| | bpm; baseline standing SBP 148.4 mm Hg, DBP 100.9 mm Hg; moexipril 15 mg: n = 47 (30 males, 17 females); mean age 56.0 years; baseline sitting SBP 154.0 mm Hg, DBP 100.9 mm Hg, HR 73.6 bpm; baseline standing SBP 150.4 mm Hg, DBP 100.2 mm Hg; placebo: n = 51 (37 males, 14 females); mean age 55.3 years; baseline sitting SBP 154.2 mm Hg, DBP 101.2 mm Hg, HR 74.7 bpm; baseline standing SBP 150.9 mm Hg, DBP 101.1 mm Hg<br><br>**Interventions:** Moexipril 7.5 mg once daily; moexipril 15 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; trough sitting DBP using mercury sphygmomanometer; trough standing SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Schwarz Pharma<br><br>**Notes:** BP change and SD of change reported; endpoint SBP not reported, endpoint DBP reported, endpoint SD not reported; change in SBP data from Table 3, p. 85; change in DBP data from Table 2, p. 83 |
| Persson 1996<br>[125] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg, with a difference of 10 mm Hg or less at last 2 consecutive visits; subjects with DBP ≥ 110 mm Hg could be included directly following minimum of 7 days run-in<br><br>**Participants:** Moexipril 7.5 mg: n = 50 (21 males, 29 females); mean age 70.4 years; baseline sitting SBP 173 mm Hg, DBP 102 mm Hg, HR 76.7 bpm; moexipril 15 mg: n = 53 (31 males, 22 females); mean age 69.2 years; baseline sitting SBP 169 mm Hg, DBP 102 mm Hg, HR 73.9 bpm; placebo: n = 48 (33 males, 15 females); mean age 70.7 years; baseline sitting SBP 172 mm Hg, DBP 103 mm Hg, HR 72.7 bpm<br><br>**Interventions:** Moexipril 7.5 mg once daily; moexipril 15 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; placebo-corrected adjusted change from baseline in peak sitting DBP using mercury |

| Study | Study Description |
|---|---|
| | sphygmomanometer; WDAE<br><br>**Funding source:** Schwarz Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint SBP not reported, endpoint DBP reported, endpoint SD not reported; change in trough BP data from Table 2, p. 261; placebo-corrected change in peak DBP data from Table 4, p. 262; endpoint BP data used instead of weighted mean of BP change for 3 measurements (at weeks 4,6,8) because N values not reported for weeks 4 and 6 |
| White 1995<br>[126] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Moexipril 7.5 mg: n = 16 (12 males, 4 females); mean age 56 (12) years; baseline sitting SBP 161 (12) mm Hg, DBP 103 (4) mm Hg, HR 76 (8) bpm; moexipril 15 mg: n = 18 (16 males, 2 females); mean age 58 (9) years; baseline sitting SBP 157 (13) mm Hg, DBP 104 (4) mm Hg, HR 78 (13) bpm; placebo: n = 17 (15 males, 2 females); mean age 50 (12) years; baseline sitting SBP 149 (17) mm Hg, DBP 106 (4) mm Hg, HR 77 (8) bpm<br><br>**Interventions:** Moexipril 7.5 mg once daily; moexipril 15 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough sitting HR<br><br>**Funding source:** Schwarz Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; change in BP data from Table II, p. 235 |

**Table 2.10: Characteristics of included studies evaluating perindopril**

| Study | Study Description |
|---|---|
| Brown 1990<br>[127] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 95-115 mm Hg |

| Study | Study Description |
|---|---|
| | **Participants:** All patients: n = 40 (19 males, 21 females); mean age 58 years; baseline upright SBP 154 (15) mm Hg, DBP 102 (7) mm Hg<br><br>**Interventions:** Perindopril 4 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough erect SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Servier<br><br>**Notes:** BP change and SEM of change reported, endpoint BP and SD not reported; calculated SD of change from N and SEM of change; BP data from Table 2, p. 329 |
| Chrysant 1993 [128] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 16 weeks total, forced titration every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br><br>**Participants:** Perindopril 4-16 mg once daily: n = 117 (65 males, 52 females); mean age 55 (10) years; baseline upright SBP 154 (15) mm Hg, DBP 102 (7) mm Hg; baseline supine SBP 157 (16) mm Hg, DBP 100 (5) mm Hg; perindopril 2-8 mg twice daily: n = 113 (73 males, 40 females); mean age 53 (12) years; baseline upright SBP 150 (15) mm Hg, DBP 101 (6) mm Hg; baseline supine SBP 152 (15) mm Hg, DBP 100 (4) mm Hg; placebo: n = 59 (45 males, 15 females); mean age 51 (12) years; baseline upright SBP 161 (14) mm Hg, DBP 103 (8) mm Hg; baseline supine SBP 153 (10) mm Hg, DBP 101 (5) mm Hg<br><br>**Interventions:** Perindopril 4, 8, 12, 16 mg once daily; perindopril 2, 4, 6, 8 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Once daily dosing: upright and supine SBP/DBP 24 ± 2 h after last dose; twice daily dosing: upright and supine SBP/DBP 12 ± 2 h after last dose; WDAE<br><br>**Funding source:** RW Johnson Pharma<br><br>**Notes:** Used week 4 supine data only; BP change change reported, SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for |

| Study | Study Description |
|---|---|
| | SD of change; BP data from Figure 1, p. 481; BP mreasurement device not reported |
| Luccioni 1988 [129] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean supine DBP ≥ 95 mm Hg<br><br>**Participants:** All patients: n = 40 (31 males, 9 females); mean age 56.6 (9.5) years; baseline BP not reported for all patients<br><br>**Interventions:** Perindopril 2 mg once daily; perindopril 4 mg once daily; perindopril 8 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Supine SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and endpoint SE reported, calculated endpoint SD from N and endpoint SE, imputed endpoint SD for SD of change; BP data from Figure 2, p. 1133 |
| Myers 1996 [130] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br><br>**Participants:** Perindopril 2 mg: n = 62 (39 males, 23 females); mean age 51 (16) years; baseline SBP/DBP not reported for all 62 patients; perindopril 4 mg: n = 57 (32 males, 25 females); mean age 51 (15) years; baseline SBP/DBP not reported for all 57 patients; perindopril 8 mg: n = 59 (32 males, 27 females); mean age 51 (15) years; baseline SBP/DBP not reported for all 59 patients; perindopril 16 mg: n = 57 (35 males, 22 females); mean age 51 (15) years; baseline SBP/DBP not reported for all 57 patients; placebo: n = 58 (30 males, 28 females); mean age 53 (15) years; baseline SBP/DBP not reported for all 58 patients<br><br>**Interventions:** Perindopril 2 mg once daily; perindopril 4 mg once daily; perindopril 8 mg once daily; perindopril 16 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; mean change from baseline in peak supine SBP/DBP using mercury sphygmomanometer; |

| Study | Study Description |
|---|---|
| | WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported, baseline SEM reported, calculated baseline SD from N and baseline SEM, imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; BP data from Table 2, p. 1193 |
| Overlack 1994 [131]<br>Multiple publications:<br>Bonner 1993 [132]<br>Middeke 1994 [133]<br>Overlack 1993 [134]<br>Stumpe 1992 [135]<br>Stumpe 1993 [136] | **Design:** Placebo run-in period: 3 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-104 mm Hg<br><br>**Participants:** Perindopril 4 mg: n = 253 (130 males, 123 females); mean age 59.3 (11.1) years; baseline SBP 161.7 (17.5) mm Hg, DBP 99.4 (4.8) mm Hg, HR 78.5 (14.3) bpm; placebo: n = 237 (133 males, 104 females); mean age 59.1 (10.8) years; baseline SBP 160.3 (16.9) mm Hg, DBP 99.5 (4.6) mm Hg, HR 79.3 (13.9) bpm<br><br>**Interventions:** Perindopril 4 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using automatic device; HR<br><br>**Funding source:** Servier<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SEM reported, calculated endpoint SD from N and endpoint SEM, imputed endpoint SD for SD of change; BP data from Table III, p. 129 |
| Reimann 1995 [137] | **Design:** Placebo run-in period: 3 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean DBP 95-104 mm Hg<br><br>**Participants:** Perindopril 4 mg: n = 27 (20 males, 7 females); mean age 54 (9.8) years; baseline sitting SBP 161.3 (12.5) mm Hg, DBP 100.4 (3.8) mm Hg; placebo: n=26 (14 males, 12 females); mean age 55 (8.5) years; baseline sitting SBP 159.6 (17.3) mm Hg, DBP 100.7 (3.2) mm Hg<br><br>**Interventions:** Perindopril 4 mg once daily; placebo<br><br>**Primary and secondary outcomes:** SBP/DBP using mercury sphygmomanometer; WDAE |

| Study | Study Description |
|---|---|
| | **Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 3, p. 190; time of BP measurement not reported |

**Table 2.11: Characteristics of included studies evaluating quinapril**

| Study | Study Description |
|---|---|
| Maclean 1989<br>[138] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks total, forced titration every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP ≥ 95 mm Hg<br><br>**Participants:** Quinapril once daily: n = 91 (64 males, 27 females); median age 49 years; baseline SBP 163 mm Hg, DBP 107 mm Hg; quinapril twice daily: n = 90 (61 males, 29 females); median age 51 years; baseline SBP 164 mm Hg, DBP 106 mm Hg; placebo: n = 89 (56 males, 33 females); median age 52 years; baseline SBP 162 mm Hg, DBP 105 mm Hg<br><br>**Interventions:** Quinapril 20, 40, 80 mg once daily; quinapril 20, 40, 80 mg twice daily (2 capsules taken 12 h apart); placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 BP data only; BP change and SE of change reported, endpoint BP and SD not reported, calculated SD of change from N and change SE; BP data from Table III, p. 375 |
| Yebes 1993<br>[139] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg<br><br>**Participants:** Quinapril: n = 10; mean age 55 (14.9) years; baseline SBP 161 (22.2) mm Hg, DBP 105 (5.6) mm Hg; placebo: n = 11; mean age 50 (9.9) years; baseline SBP 154 (20.6) mm Hg, DBP 103 (5.0) mm Hg |

| Study | Study Description |
|---|---|
| | **Interventions:** Quinapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in sitting SBP/DBP<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change reported, endpoint BP and SD reported; SBP data from Table IA, p. 321, DBP data from Table IIA, p. 323; BP measurement device not reported; time of BP measurement not reported |

**Table 2.12: Characteristics of included studies evaluating ramipril**

| Study | Study Description |
|---|---|
| Homuth 1993 [140] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean DBP 100-115 mm Hg<br><br>**Participants:** Ramipril 2.5 mg: n = 40 (26 males, 14 females); mean age 47 (10) years; baseline SBP 159 (15) mm Hg, DBP 107 (5) mm Hg; ramipril 5 mg: n = 40 (23 males, 17 females); mean age 48 (8) years; baseline SBP 159 (13) mm Hg, DBP 107 (6) mm Hg; ramipril 10 mg: n = 40 (24 males, 16 females); mean age 47 (9) years; baseline SBP 160 (14) mm Hg, DBP 109 (5) mm Hg; placebo: n = 40 (22 males, 18 females); mean age 46 (10) years; baseline SBP 161 (17) mm Hg, DBP 109 (5) mm Hg<br><br>**Interventions:** Ramipril 2.5 mg once daily; ramipril 5 mg once daily; ramipril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Cassella AG<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; BP data from Figures 1 and 2, p. 669 |
| Kostis 1991 [141] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3 |

| Study | Study Description |
|---|---|
| | **Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br><br>**Participants:** Ramipril 1.25 mg: n = 44 (18 males, 26 females); mean age 52.3 years; baseline SBP 159 (15) mm Hg, DBP 99.9 (3.7) mm Hg; ramipril 2.5 mg: n = 43 (27 males, 16 females); mean age 49.4 years; baseline supine DBP 99.8 (3.7) mm Hg; ramipril 5 mg: n = 43 (23 males, 20 females); mean age 53.4 years; baseline supine DBP 100.7 (5.1) mm Hg; ramipril 10 mg: 44 (29 males, 15 females); mean age 52.1 years; baseline supine DBP 101.2 (4.4) mm Hg; placebo: n = 42 (22 males, 20 females); mean age 51.3 years; baseline supine DBP 99.3 (3.6) mm Hg<br><br>**Interventions:** Ramipril 1.25 mg once daily; ramipril 2.5 mg once daily; ramipril 5 mg once daily; ramipril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; BP data from Table 3, p. 13, SD data from Figures II and III, p. 12 |
| McCarron 1991 [142] | **Design:** Placebo run-in period: 3-4 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 100-114 mm Hg<br><br>**Participants:** Ramipril 10 mg: n = 67 (44 males, 23 females); mean age 53.8 (9.8) years; baseline supine SBP 152.7 (11.4) mm Hg, DBP 102.9 (3.0) mm Hg; placebo: n = 33 (23 males, 10 females); mean age 52.3 (11.7) years; baseline supine SBP 151.9 (13.2) mm Hg, DBP 102.1 (3.0) mm Hg<br><br>**Interventions:** Ramipril 10 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SE reported, calculated SD of change from N and SE of change; BP data from Table III, p. 740 |

| Study | Study Description |
|---|---|
| Scholze 1999<br>[143] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine DBP 100-115 mm Hg<br>**Participants:** All patients: n = 507 (327 males, 180 females); mean age 50.2 years; baseline SBP/DBP not reported<br>**Interventions:** Ramipril 2.5 mg once daily; ramipril 5 mg once daily; ramipril 10 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer<br>**Funding source:** Hoechst AG<br>**Notes:** BP change and SEM of change reported, endpoint BP and SD not reported; calculated SD of change from N and change SE; BP data from Table 1, p. 1453 |
| Trevisan 1995<br>[144] | **Design:** Placebo run-in period: Not reported. Treatment duration: 24 weeks total, report BP at 4 weeks<br>**Quality:** Cochrane method = B; Jadad score = 4<br>**Inclusion criteria:** No minimal BP inclusion criteria, trial included both hypertensive and non-hypertensive patients<br>**Participants:** All patients (normotensive and hypertensive) with non-insulin-dependent diabetes mellitus: ramipril 1.25 mg: n = 60 (44 males, 16 females); mean age 56 (7) years; baseline SBP 147 (15) mm Hg, DBP 90 (6) mm Hg; placebo: n = 62 (50 males, 12 females); mean age 58 (7) years; baseline SBP 151 (14) mm Hg, DBP 91 (6) mm Hg; Subgroup of patients with BP ≥ 160/95 mm Hg: ramipril 1.25 mg: n = 19; baseline SBP 156 (12) mm Hg, DBP 95 (4) mm Hg; placebo: n = 24; baseline SBP 161 (9) mm Hg, DBP 95 (3) mm Hg<br>**Interventions:** Ramipril 1.25 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in sitting SBP/DBP using mercury sphygmomanometer; WDAE<br>**Funding source:** Hoechst AG<br>**Notes:** Used week 4 BP data only; used BP data from subgroup with BP ≥ |

| Study | Study Description |
|---|---|
| | 160/95 mm Hg; BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD of change; BP data from Table 5, p. 881; time of BP measurement not reported |
| Villamil 1987 [145] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean standing DBP 95-120 mm Hg<br>**Participants:** Ramipril 2.5 mg: n = 28 (12 males, 16 females); median age 54 years; baseline SBP 162.0 mm Hg, DBP 101.1 mm Hg; ramipril 5 mg: n = 29 (11 males, 18 females); median age 53 years; baseline SBP 166.8 mm Hg, DBP 103.2 mm Hg; placebo: n = 27 (15 males, 12 females); median age 52 years; baseline SBP 166.6 mm Hg, DBP 101.5 mm Hg<br>**Interventions:** Ramipril 2.5 mg once daily; ramipril 5 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br>**Funding source:** Hoechst AG<br>**Notes:** BP change and SEM of change reported, endpoint BP and SD not reported; calculated SD of change from N and change SE; BP data from Tables III and IV, p. 112D |

**Table 2.13: Characteristics of included studies evaluating spirapril**

| Study | Study Description |
|---|---|
| Fairhurst 1994 [146] | **Design:** Placebo run-in period: 3-4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg<br>**Participants:** All patients: n = 283 (157 males, 126 females); mean age 55 years; spirapril 3 mg: n = 55; spirapril 6 mg: n = 61; spirapril 12 mg: n = 58; spirapril 24 mg: n = 49; placebo: n = 60<br>**Interventions:** Spirapril 3 mg once daily; spirapril 6 mg once daily; spirapril |

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|---|---|
| | 12 mg once daily; spirapril 24 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Sandoz Pharma<br><br>**Notes:** BP change reported, SD of change not reported; endpoint BP and SD of change not reported; imputed overall trial mean SBP/DBP SD of change; BP data from Figure 1, p. 78 |
| Guitard 1994 [147] | **Design:** Placebo run-in period: 3-4 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-119 mm Hg<br><br>**Participants:** Spirapril 6 mg: n = 66 (32 males, 34 females); mean age 58 (11) years; baseline sitting SBP 171 (12) mm Hg, DBP 106 (4) mm Hg, HR 76 (10) bpm; spirapril 12 mg: n = 64 (23 males, 41 females); mean age 58 (9) years; baseline sitting SBP 168 (14) mm Hg, DBP 105 (4) mm Hg, HR 73 (9) bpm; spirapril 24 mg: n = 66 (35 males, 31 females); mean age 58 (11) years; baseline sitting SBP 170 (12) mm Hg, DBP 106 (4) mm Hg, HR 74 (9) bpm; placebo: n = 64 (24 males, 40 females); mean age 57 (11) years; baseline sitting SBP 167 (11) mm Hg, DBP 105 (3) mm Hg, HR 73 (9) bpm<br><br>**Interventions:** Spirapril 6 mg once daily; spirapril 12 mg once daily; spirapril 24 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Sandoz Pharma<br><br>**Notes:** BP change reported, SD of change reported but values are too low, endpoint SBP not reported, endpoint DBP reported, endpoint SD not reported; change in trough BP data from Table II, p. 83; SD of change data from Figure 2, p. 85; change in peak DBP data in subgroup of patients (from one study center) in Figure 3, p. 85; Table II provides data for both efficacy and intention-to-treat (ITT) analysis, ITT analysis BP data used instead of efficacy analysis BP data; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change |
| Guitard 1997 [97] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks total, titration-to-response at 4 weeks |

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|---|---|
| | **Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean DBP 100-115 mm Hg<br><br>**Participants:** Spirapril 6 mg: n = 101 (50 males, 50 females); mean age 58.0 (7.9) years; baseline SBP 161.8 (16.3) mm Hg, DBP 99.7 (6.6) mm Hg; enalapril 5 mg: n = 101 (54 males ,47 females); mean age 56.2 (9.7) years; baseline SBP 163.2 (16.4) mm Hg, DBP 99.5 (6.1) mm Hg; placebo: n = 50 (32 males, 18 females); mean age 56.5 (8.2) years; baseline SBP 161.3 (18.2) mm Hg, DBP 98.2 (6.9) mm Hg<br><br>**Interventions:** Spirapril 6 mg once daily; enalapril 5 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting DBP; adjusted mean change from baseline in peak sitting DBP<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Used week 4 BP data only; BP change reported, SD of change not reported, endpoint BP reported, endpoint SD not reported; imputed overall trial mean DBP SD of change; DBP data from Table 5, p. 455; BP measurement device not reported |
| Pittrow 1997<br>[148] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 12 weeks total, titration-to-response at 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-114 mm Hg<br><br>**Participants:** Spirapril 3 mg: n = 52 (32 males, 20 females); mean age 55.8 years; baseline sitting SBP 159.0 mm Hg, DBP 104.6 mm Hg (trough data); baseline sitting SBP 156.7 mm Hg, DBP 103.4 mm Hg (peak data); spirapril 6 mg: n = 52 (28 males, 24 females); mean age 53.6 years; baseline sitting SBP 159.0 mm Hg, DBP 104.8 mm Hg (trough data); baseline sitting SBP 157.6 mm Hg, DBP 102.9 mm Hg (peak data); placebo: n = 26 (18 males, 8 females); mean age 54.2 years; baseline sitting SBP 154.2 mm Hg, DBP 104.1 mm Hg (trough data); baseline sitting SBP 151.6 mm Hg, DBP 102.8 mm Hg (peak data)<br><br>**Interventions:** Spirapril 3 mg once daily; spirapril 6 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in peak sitting SBP/DBP using mercury sphygmomanometer; |

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|---|---|
| | WDAE<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change reported, endpoint BP reported, endpoint SD not reported; change in trough and peak BP data from Table 2A, p. 624 |

**Table 2.14: Characteristics of included studies evaluating temocapril**

| Study | Study Description |
|---|---|
| Lerch 1999<br><br>[149] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 90-115 mm Hg<br><br>**Participants:** Temocapril 20 mg: n = 19 (13 males, 6 females); mean age 57.6 (8.3) years; baseline SBP 162 (22) mm Hg, DBP 98 (9) mm Hg; placebo: n = 11 (8 males, 3 females); mean age 56.1 (5.6) years; baseline SBP 151 (13) mm Hg, DBP 97 (7) mm Hg<br><br>**Interventions:** Temocapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SE reported, calculated endpoint SD from N and endpoint SE, imputed endpoint SD for SD of change; BP data from Table 1, p. 529 |

**Table 2.15: Characteristics of included studies evaluating trandolapril**

| Study | Study Description |
|---|---|
| De Bruijn 1994<br><br>[150] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine and standing DBP 95-115 mm Hg<br><br>**Participants:** Trandolapril 0.5 mg: n = 41 (17 males, 24 females); mean age 49 (13) years; baseline SBP 163.8 (12.8) mm Hg, DBP 99.5 (5.8) mm Hg; trandolapril 1 mg: n = 42 (8 males, 38 females); mean age 48 (13) years; baseline SBP 159.9 (14.3) mm Hg, DBP 99.9 (5.2) mm Hg; trandolapril 2 |

| Study | Study Description |
|---|---|
| | mg: n = 43(23 males, 20 females); mean age 46 (13) years; baseline SBP 161.1 (13.1) mm Hg, DBP 99.8 (5.9) mm Hg; placebo: n = 44 (18 males, 26 females); mean age 50 (7) years; baseline SBP 157.3 (16.6) mm Hg, DBP 99.2 (6.0) mm Hg<br><br>**Interventions:** Trandolapril 0.5 mg once daily; trandolapril 1 mg once daily; trandolapril 2 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Roussel Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; BP data from Figures 1 and 2, pp. S61-S62 |
| DeQuattro 1997 [151]<br>Multiple publications: DeQuattro 1997 [152] Levine 1997 [153] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** All patients (trandolapril monotherapy, verapamil monotherapy + verapamil/trandolapril combination treatment arms): n = 726 (456 males, 270 females); mean age 54.7 (10.9) years; baseline sitting SBP 151.8 (16.2) mm Hg, DBP 100.4 (6.1) mm Hg; trandolapril 0.5 mg: n = 41; baseline SBP 155.4 (15.7) mm Hg, DBP 100.3 (4.4) mm Hg; trandolapril 2 mg: n = 67; baseline SBP 151.4 (16.5) mm Hg, DBP 99.8 (4.6) mm Hg; trandolapril 8 mg: n = 43; baseline SBP 150.7 (16.3) mm Hg, DBP 99.5 (4.2) mm Hg; placebo: n = 53; baseline SBP 154.8 (15.1) mm Hg, DBP 100.3 (4.6) mm Hg;<br><br>**Interventions:** Trandolapril 0.5 mg once daily; trandolapril 2 mg once daily; trandolapril 8 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Knoll Pharma<br><br>**Notes:** Supine baseline BP reported in duplicate publication for each treatment arm; BP change reported, SD of change not reported, endpoint BP and SD not reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; data from Table II, p. 367; |

| Study | Study Description |
|---|---|
| Kohlmann Jr 1999 [154]<br>Duplicate publication: Schnaper 1991 [155] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean DBP 95-115 mm Hg<br>**Participants:** Trandolapril 2 mg: n = 135 (55 males, 80 females); mean age 53.1 (11.3) years; baseline SBP 157.3 (15) mm Hg, DBP 101.0 (6.3) mm Hg, HR 75.6 (9.1) bpm; placebo: n = 135 (55 males, 80 females); mean age 53.1 (11.3) years; baseline SBP 156.1 (18) mm Hg, DBP 100.3 (6.6) mm Hg, HR 75.6 (9.1) bpm<br>**Interventions:** Trandolapril 2 mg once daily; placebo<br>**Primary and secondary outcomes:** SBP/DBP<br>**Funding source:** Not reported<br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; endpoint BP (week 8) data from text, p. 549; BP data for weeks 5 and 8 provided in Figures 1 and 2, p. 550; BP measurement device not reported |
| Mancia 1992 [156]<br>Duplicate publication: Ravogli 1994 [157] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine and standing DBP ≥ 95 mm Hg<br>**Participants:** Trandolapril 2 mg: n = 42 (31 males, 11 females); mean age 51.4 (9.7) years; baseline supine SBP 159.8 (12.8) mm Hg, DBP 102.4 (5.1) mm Hg, HR 72.1 (8.3) bpm; placebo: n = 20 (15 males, 5 females); mean age 51.1 (7.6) years; baseline supine SBP 158.0 (13.5) mm Hg, DBP 102.3 (4.8) mm Hg, HR 73.9 (8.3) bpm<br>**Interventions:** Trandolapril 2 mg once daily; placebo<br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer; trough supine HR; WDAE<br>**Funding source:** Rossel Pharma<br>**Notes:** BP change and SD of change not reported, endpoint BP and SE reported; calculated endpoint SD from N and endpoint SE, imputed endpoint SD for SD of change; BP data from Table II, p. 62D |

| Study | Study Description |
|---|---|
| Mancia 1997<br>[158]<br>Duplicate publication:<br>Burris 1991 [159] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean sitting DBP 100-110 mm Hg<br>**Participants:** Trandolapril 1 mg: n = 50; mean age 51 (10) years; baseline sitting SBP 159.3 (12.4) mm Hg, DBP 103.6 (3.1) mm Hg, HR 73.2 (10.6) bpm; placebo: n = 51; mean age 52 (9) years; baseline sitting SBP 158.2 (13.5) mm Hg, DBP 103.5 (3.4) mm Hg, HR 75.4 (8.2) bpm<br>**Interventions:** Trandolapril 1 mg once daily; placebo<br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer; peak sitting SBP/DBP using mercury sphygmo-manometer; trough sitting HR; WDAE<br>**Funding source:** Not reported<br>**Notes:** BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD for SD of change; trough BP data from Table 1, p. 493; peak BP data (using 24h ambulatory BP monitoring) in Figure 3, p. 496 |
| Messerli 1998<br>[160] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br>**Participants:** Trandolapril 4 mg: n = 159 (106 males, 53 females); mean age 54.3 years; baseline SBP 151.8 (14.8) mm Hg, DBP 101.3 (5.0) mm Hg; placebo: n = 152 (103 males, 49 females); mean age 53.8 years; baseline SBP 153.6 (13.4) mm Hg, DBP 100.5 (4.5) mm Hg<br>**Interventions:** Trandolapril 4 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br>**Funding source:** Knoll Pharma<br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; SD of change values reported are low; imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Table 2, p. 325 |

| Study | Study Description |
|---|---|
| New 2000<br>[161] | **Design:** Placebo run-in period: None. Treatment duration: 3 weeks<br>**Quality:** Cochrane method = B; Jadad score = 2<br>**Inclusion criteria:** Patients with established Type 2 DM and BP > 75th percentile for age and sex, taking no anti-hypertensive medication<br>**Participants:** Trandolapril 4 mg: n = 12 (10 males, 2 females); mean age 58 (11) years; baseline SBP 168 (13) mm Hg, DBP 98 (10) mm Hg; placebo: n = 12 (9 males, 3 females); mean age 60 (12) years; baseline SBP 165 (14) mm Hg, DBP 93 (6) mm Hg<br>**Interventions:** Trandolapril 4 mg once daily; placebo<br>**Primary and secondary outcomes:** Trough supine SBP/DBP using mercury sphygmomanometer<br>**Funding source:** Hoechst Marion Rousell<br>**Notes:** BP change and SD of change not reported; endpoint BP and SD reported; imputed endpoint SD for SD of change; SBP/DBP data from Figure 1, p. 137 |
| Scholze 1998<br>[162] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg, which differed by less than 10 mm Hg from that observed on the previous run-in visit<br>**Participants:** Trandolapril 0.5-2 mg: n = 85; baseline SBP/DBP not reported; placebo: n = 30; baseline SBP/DBP not reported<br>**Interventions:** Trandolapril 0.5 mg once daily; trandolapril 1 mg once daily; trandolapril 2 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br>**Funding source:** Knoll AG<br>**Notes:** Adjusted and non-adjusted BP data reported; non-adjusted BP entered in Revman; BP change reported, SD of change not reported; 95% confidence interval of change reported; endpoint BP and SD not reported; calculated SD of change from 95% CI of change; BP data from Table 1, p. 493 |

| Study | Study Description |
|---|---|
| Vaur 1998<br>[163] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 4 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br>**Participants:** Trandolapril 2 mg: n = 24 (15 males, 9 females); mean age 56 (10) years; baseline sitting SBP 163 (16) mm Hg, DBP 101 (6) mm Hg; placebo: n = 10 (5 males, 5 females); mean age 53 (12) years; baseline SBP 157 (14) mm Hg, DBP 100 (7) mm Hg<br>**Interventions:** Trandolapril 2 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br>**Funding source:** Roussel Pharma<br>**Notes:** BP change and SD of change reported; endpoint BP and SD not reported; SBP/DBP data from Table 3, p. 110 |
| Weir 1995<br>[164]<br>Duplicate publication:<br>Weir 1998 [165] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg during both of final 2 consecutive weeks of run-in<br>**Participants:**<br>Black and white patients reported in Weir 1995:<br>Trandolapril 1 mg: n = 51 (33 males, 18 females); mean age 58.3 (11.4) years; baseline sitting SBP 154.8 (15.0) mm Hg, DBP 100.3 (4.3) mm Hg; trandolapril 2 mg: n = 53 (36 males, 17 females); mean age 57.3 (10.9) years; baseline sitting SBP 151.9 (13.1) mm Hg, DBP 101.7 (5.1) mm Hg; trandolapril 4 mg: n = 53 (28 males, 25 females); mean age 53.0 (12.4) years; baseline sitting SBP 147.6 (13.8) mm Hg, DBP 99.9 (4.4) mm Hg; placebo: n = 50 (35 males, 15 females); mean age 60.6 (9.9) years; baseline SBP 152.1 (14.9) mm Hg, DBP 100.9 (5.0) mm Hg<br>Only black patients reported in Weir 1998 (duplicate publication):<br>Trandolapril 0.25 mg: n = 23 (12 males, 11 females); mean age 48.6 (12.7) years; baseline supine SBP 159.1 (13.5) mm Hg, DBP 101.7 (5.3) mm Hg; trandolapril 0.5 mg: n = 22 (9 males, 13 females); mean age 49.4 (12.3) |

| Study | Study Description |
|---|---|
| | years; baseline supine SBP 152.1 (11.7) mm Hg, DBP 101.6 (4.9) mm Hg; trandolapril 1 mg: n = 23 (7 males, 16 females); mean age 52.7 (11.1) years; baseline supine SBP 150.7 (13.1) mm Hg, DBP 99.7 (3.5) mm Hg (same patients as Weir 1995); trandolapril 2 mg: n = 22 (10 males, 12 females); mean age 53.0 (10.2) years; baseline supine SBP 146.1 (11.4) mm Hg, DBP 99.1 (3.2) mm Hg (same patients as Weir 1995); trandolapril 4 mg: n = 60 (28 males, 32 females); mean age 53.6 (10.8) years; baseline supine SBP 156.2 (16.1) mm Hg, DBP 101.7 (4.9) mm Hg (same patients as Weir 1995); trandolapril 8 mg: n = 38 (19 males, 19 females); mean age 55.3 (11.9) years; baseline supine SBP 158.7 (19.3) mm Hg, DBP 101.4 (4.3) mm Hg; trandolapril 12 mg: n = 38 (19 males, 19 females); mean age 53.1 (13.5) years; baseline supine SBP 153.0 (12.4) mm Hg, DBP 100.9 (4.1) mm Hg; trandolapril 16 mg: n = 36 (15 males, 21 females); mean age 54.4 (12.2) years; baseline supine SBP 159.5 (17.3) mm Hg, DBP 100.5 (3.7) mm Hg; placebo: n = 60 (27 males, 33 females); mean age 53.5 (10.0) years; baseline supine SBP 155.7 (15.5) mm Hg, DBP 100.6 (4.2) mm Hg<br><br>**Interventions:** Trandolapril 0.25 mg once daily (black patients only); trandolapril 0.5 mg once daily (black patients only); trandolapril 1 mg once daily (black and white patients); trandolapril 2 mg once daily (black and white patients); trandolapril 4 mg once daily (black and white patients); trandolapril 8 mg once daily (black patients only); trandolapril 12 mg once daily (black patients only); trandolapril 16 mg once daily (black patients only); placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer (Trandolapril 1, 2, 4 mg treatment arms); mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer (Trandolapril 0.25, 0.5, 8, 12, 16 mg treatment arms); WDAE<br><br>**Funding source:** Knoll Pharma<br><br>**Notes:** Weir 1995: BP change and SE of change reported; calculated SD of change from N and SE of change; endpoint BP and SD not reported; SBP/DBP data from Table 2, p. 126; Weir 1998: BP change and SE of change reported for trandalopril groups; SBP SE of change in placebo group not reported; DBP SE of change in placebo group reported; imputed baseline SBP SE for SE of change; SBP/DBP data from Table 2, p. 191 |

Baseline characteristics of the 92 included studies are provided in Table 2.16. A total of 12 954 participants with a mean age of 54.4 years and baseline blood pressure of 157.1/101.2 mm Hg were treated for a mean duration of 6.2 weeks. In most cases, the number of patients treated with an ACE inhibitor was larger than the number of placebo-treated patients because many of the included studies have multiple treatment arms comparing different doses of an ACE inhibitor with a single placebo arm.

**Table 2.16: Overview of the 92 included studies evaluating ACE inhibitors as monotherapy**

| Drug<br>Daily dose range<br>Total studies | Number of ACEI patients | Number of placebo patients | Mean age of patients | Mean baseline BP<br>Pulse pressure (mm Hg) | Mean duration of treatment (weeks) |
|---|---|---|---|---|---|
| benazepril<br>2 - 80 mg<br>7 studies | 591 | 335 | 56.3 | 159.5/103.5<br>56.0 | 6.0 |
| captopril<br>37.5 - 200 mg<br>6 studies | 660 | 383 | 54.9 | 155.0/100.1<br>54.9 | 6.5 |
| cilazapril<br>0.5 - 10 mg<br>14 studies | 1054 | 448 | 53.3 | 153.5/101.0<br>52.5 | 4.9 |
| enalapril<br>5 - 20 mg<br>19 studies | 1477 | 1331 | 54.2 | 157.5/100.5<br>57.0 | 6.5 |
| fosinopril<br>2.5 - 40 mg<br>6 studies | 481 | 168 | 52.5 | 152.1/101.2<br>50.9 | 5.0 |
| imidapril<br>5 - 40 mg<br>1 study | 127 | 35 | 51.9 | 160.7/101.5<br>59.2 | 4.0 |
| lisinopril<br>1.25 - 80 mg<br>5 studies | 484 | 357 | 55.2 | 154.5/101.8<br>52.7 | 5.7 |
| moexipril<br>7.5 - 15 mg<br>4 studies | 274 | 159 | 60.5 | 160.4/101.7<br>58.7 | 10.7 |
| perindopril<br>2 - 16 mg<br>6 studies | 658 | 396 | 55.9 | 159.4/99.9<br>59.5 | 7.1 |
| quinapril<br>20 mg<br>3 studies | 99 | 97 | 52.6 | 161.7/105.6<br>56.1 | 4.0 |
| ramipril<br>1.25 – 10 mg<br>6 studies | 548 | 199 | 51.2 | 156.6/100.9<br>55.7 | 6.6 |
| spirapril<br>3 - 24 mg<br>4 studies | 586 | 189 | 52.3 | 164.3/103.5<br>60.8 | 5.6 |

| Drug<br>Daily dose range<br>Total studies | Number of ACEI patients | Number of placebo patients | Mean age of patients | Mean baseline BP<br>Pulse pressure (mm Hg) | Mean duration of treatment (weeks) |
|---|---|---|---|---|---|
| temocapril<br>20 mg<br>1 study | 19 | 11 | 57.0 | 158.0/97.6<br>60.4 | 6.0 |
| trandolapril<br>0.25 – 16 mg<br>10 studies | 1152 | 636 | 53.4 | 155.4/100.7<br>54.7 | 6.1 |
| **TOTAL:**<br>92 studies<br>12 954 patients | 8210 | 4744 | 54.4 | 157.1/101.2<br>55.9 | 6.2 |

Table 2.16 demonstrates that there is sufficient RCT evidence for the various ACE inhibitors to generate dose-response curves for systolic and diastolic blood pressure reduction as well as accomplish the secondary goals of this review. These studies investigate most ACE inhibitors over a dose range that is wider than what is recommended by the manufacturers.

### 2.2.2 Imputation of missing variance data

Forty (44%) of the included trials reported the standard deviation of the change in blood pressure. These values were pooled for the ACE inhibitor and placebo groups and weighted mean estimates of the standard deviation of the change in SBP and DBP were determined. Three trials [120,147,160] were excluded from the calculation, and the weighted mean estimates were adjusted, because they reported standard deviation values that were so low they were more than 3 standard deviations away from the weighted mean SD of BP change. The weighted mean standard deviations of the change in SBP and DBP were 13.90 (SD 2.2) mm Hg and 8.1 (SD 1.4) mm Hg for the ACE inhibitor group, respectively. For the placebo group, the standard deviation of the change was 13.40 (SD 3.8) mm Hg for SBP and 7.7 (SD 2.2) mm Hg for DBP. There was no statistically significant difference between the ACE inhibitor and placebo groups for SD of SBP change, or SD of DBP change. These values were used according to the imputation hierarchy for trials that did not report SD of BP change or reported an outlier SD value.

The SD of BP change was imputed for 55 (60%) of the included studies. Of these studies, 29 (32%) were imputed using endpoint SD, 13 (14%) were imputed using

baseline SD for SBP, 11 (12%) were imputed using the weighted mean SD of SBP change from other trials, and 7 (8%), were imputed using the weighted mean SD of DBP change from other trials.

### 2.2.3 Methodological quality of included studies

The Jadad and Cochrane scales were used in this review to assess the quality of the included studies. Eighty seven (94.6%) of the included trials did not report allocation concealment, while the remaining five (5.4%) trials reported an adequate method of concealment. The Jadad score for each included study is provided in the 'Notes' section of Tables 2.2 - 2.15. Using the Jadad quality score, 75 (81.5%) of the included studies were of good quality, 2 (2.2%) were of excellent quality, and 15 (16.3%) studies were of poor quality. Removing the studies that were considered poor according to the Jadad method did not alter the results of the meta-analysis. Rather, the Jadad score was not very useful for assessing the quality of trials included in this review because its scoring criteria were similar to two of the criteria for inclusion of studies in our systematic review; the studies had to be randomized and double-blind. Thus all included studies would score at least 2 on the Jadad scale. Furthermore, it was clear to us that the Jadad and Cochrane quality assessment scales were not evaluating the methodological quality of the trials but instead the quality of reporting in the published studies.

The most crucial factor in the included studies, which is not considered in the Jadad and Cochrane quality assessment scales, is the accuracy of blood pressure measurement (and the reporting of this value). The quality of reporting of the blood pressure results in the included trials appeared to be independent of the quality of reporting of the methodology.

### 2.2.4 Dose-ranging BP lowering efficacy of individual ACE inhibitor drugs

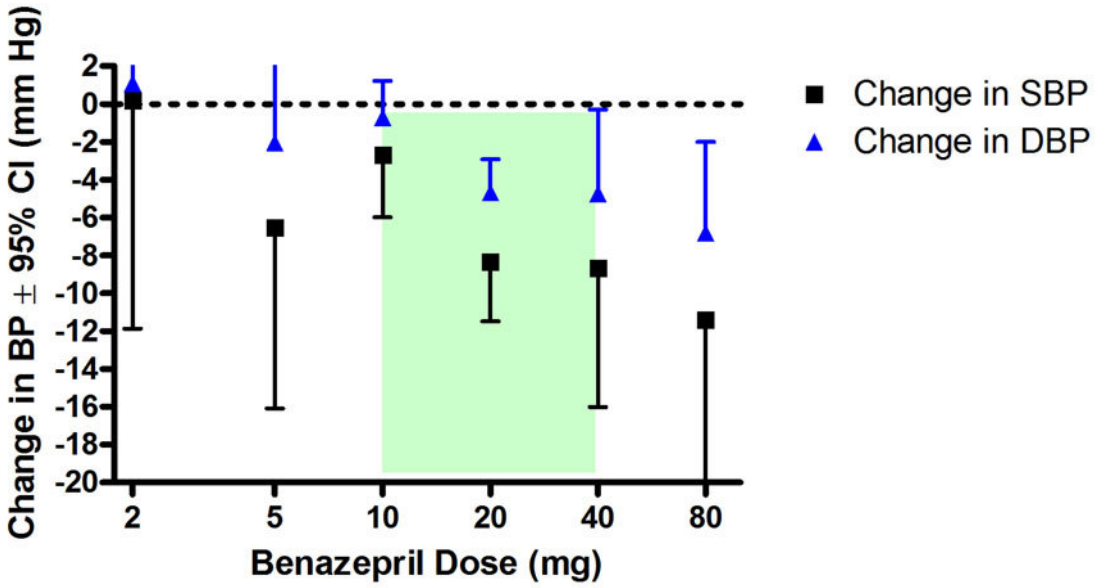
Summarized below are the dose-related trough blood pressure lowering efficacy estimates of 13 of the 14 ACE inhibitors that were administered once daily in the included studies. Captopril was administered twice or three times daily in nearly all the trials evaluating this drug. The weighted mean placebo effect across all trials was -3.2 (95% CI -3.6, -2.9; range -14.7 to 3.7) mm Hg and -3.7 (95% CI -3.9, -3.5; range -10.1 to 3.0) mm Hg for SBP and DBP, respectively. Therefore, to determine the magnitude of the

blood pressure lowering efficacy of each ACE inhibitor, a weighted mean difference from placebo (ACEI effect size minus placebo effect size) with a 95% confidence interval (in parentheses) was calculated.

#### 2.2.4.1 Dose-ranging BP lowering efficacy of benazepril

Seven of the included trials assessed benazepril at doses ranging from 2 mg/day to 80 mg/day. The log dose-response curve for benazepril is presented in Figure 2.4.

**Figure 2.4: Log dose-response curve of benazepril 2 - 80 mg/day (Shaded area represents the manufacturer's recommended dose range)**




Benazepril doses of 2 to 10 mg/day did not significantly reduce blood pressure compared with placebo. Benazepril at 20 mg/day was the lowest dose that demonstrated a significantly greater reduction in SBP and DBP as compared to placebo.

Only two trials [64,66] allowed a direct comparison analysis of the effect size for each dose and there was no statistically significant difference in the effect sizes between doses.

An indirect comparison demonstrated a statistically significant difference between the 10 and 20 mg/day groups, which is evidence of a dose-response effect for benazepril. Due to a paucity of data at 40 and 80 mg/day, reflected in the wide confidence intervals, the 20 mg/day group did not show a statistically significant difference between the 40 and

80 mg/day groups.

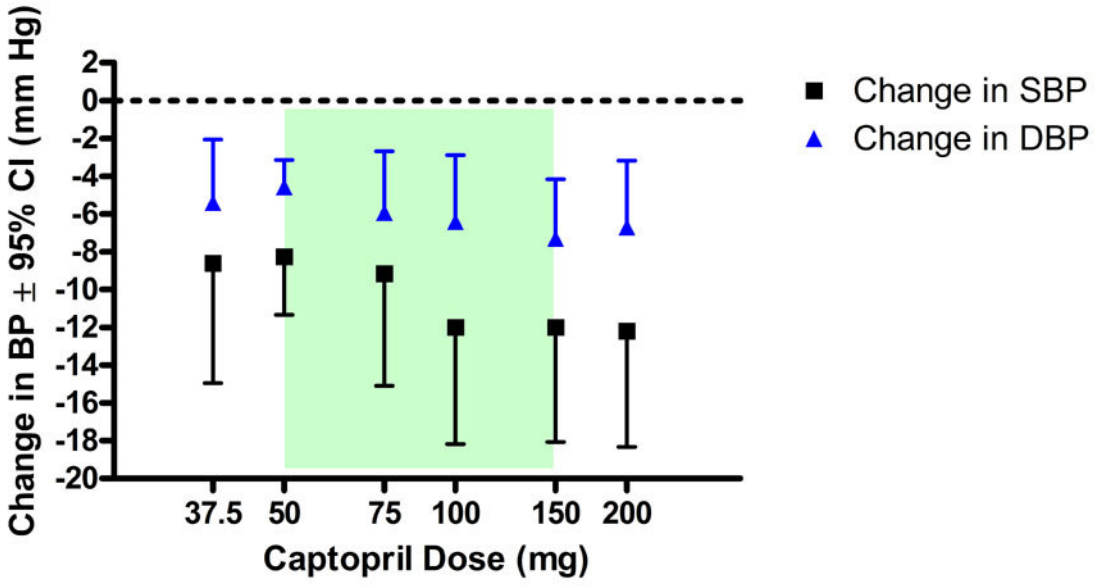
Based on the available evidence, the best estimate of the near maximal blood pressure lowering efficacy of benazepril occurs between 20 and 80 mg/day. The best estimate of the blood pressure lowering effect across this dosage range is -8.70 (95% CI: -11.43, -5.97) mm Hg for SBP and -4.92 (95% CI: -6.47, -3.36) mm Hg for DBP.

#### 2.2.4.2 Dose-ranging BP lowering efficacy of captopril

Captopril was the only ACE inhibitor that was usually prescribed as twice or three times daily dosing in the included trials. Three of the five trials assessed captopril at twice daily dosing [68,69,72], one trial at three times daily dosing [74], and one trial assessed captopril 50 mg once daily [71]. Sensitivity analyses were performed to assess the robustness of the results, which were unchanged whether the dosing was once, twice or three times daily.

All doses tested significantly lowered blood pressure compared with placebo and there was no statistically significant difference between any of the doses using indirect comparisons (Figure 2.5).

**Figure 2.5: Log dose-response curve of captopril 37.5 - 200 mg/day (Shaded area represents manufacturer's recommended dose range)**

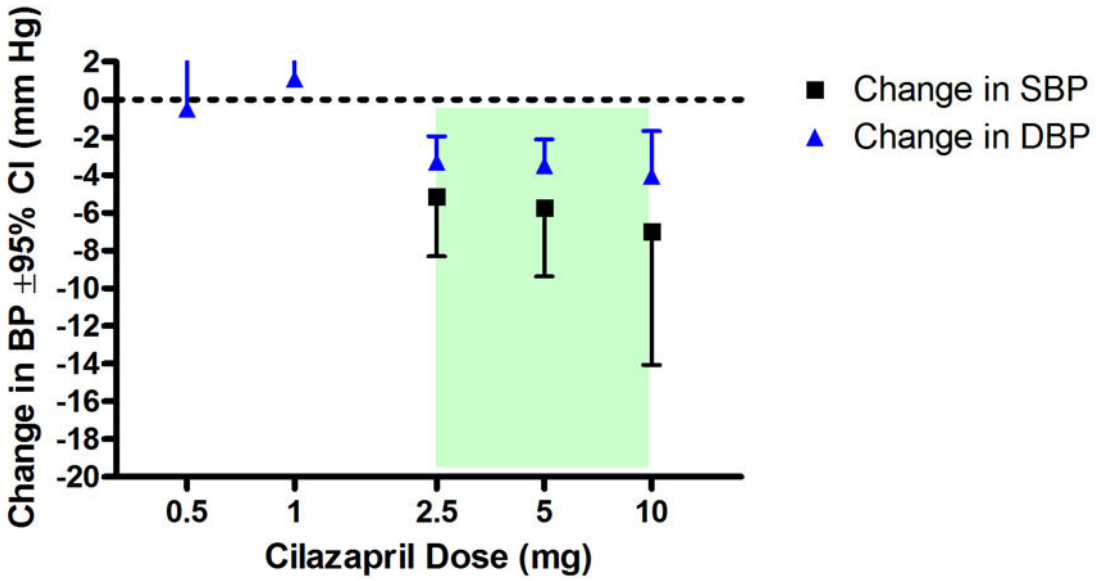


However, the paucity of data at doses other than 50 mg/day – the manufacturer's recommended starting dose – makes it difficult to adequately assess a dose-response relationship. The lowest effective dose appears to be 37.5 mg/day, the lowest dosage studied. The lowest effective dose could be lower but there are no data available below 37.5 mg/day. Based on the available evidence, the best estimate of the near maximal blood pressure lowering efficacy of captopril is -9.68 (95% CI -11.73, -7.63) mm Hg and -5.43 (95% CI -6.47, -4.40) mm Hg for SBP and DBP, respectively.

#### 2.2.4.3 Dose-ranging BP lowering efficacy of cilazapril

Nine of the included trials assessed the SBP lowering efficacy of cilazapril at doses ranging from 2.5 to 10 mg/day, whereas 14 trials assessed the effect on DBP at a wider dosage range of 0.5 to 10 mg/day (Figure 2.6).

**Figure 2.6: Log dose-response curve of cilazapril 0.5 - 10 mg/day (Shaded area represents manufacturer's recommended dose range)**




There was no statistically significant difference compared with placebo for change in DBP at 0.5 and 1 mg/day. The three doses encompassing the manufacturer's recommended range did result in a statistically significant reduction in SBP and DBP and there was no statistically significant difference between any of the three doses. This suggests that the lowest effective dose of 2.5 mg/day – which is the manufacturer's

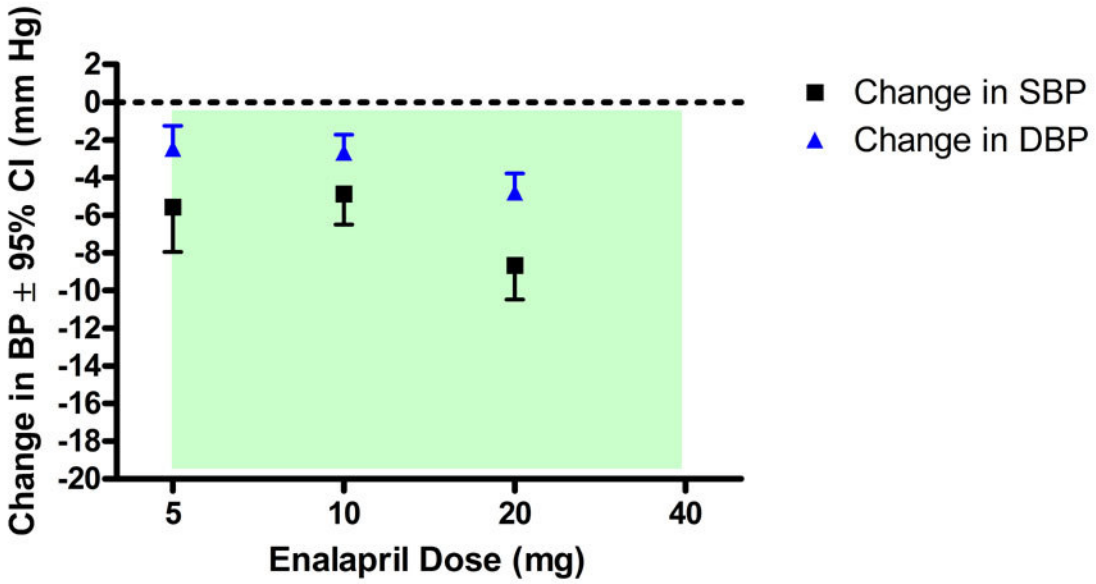
recommended starting dose – is at the plateau of the dose-response curve and thus also the lowest dose with near maximal blood pressure lowering efficacy.

The best estimate of the near maximal trough blood pressure lowering efficacy for doses of 2.5 to 10 mg/day is -5.58 (95% CI -7.84, -3.52) mm Hg and -3.50 (95% CI -4.40, -2.60) mm Hg for SBP and DBP, respectively.

#### 2.2.4.4 Dose-ranging BP lowering efficacy of enalapril

Nineteen of the included studies assessed the blood pressure lowering efficacy of enalapril from 5 to 20 mg/day but there were no data available at 40 mg/day, the manufacturer's maximum recommended daily dosage (Figure 2.7).

**Figure 2.7: Log dose-response curve of enalapril 5 - 40 mg/day (Shaded area represents manufacturer's recommended dose range)**




Compared with placebo, all doses demonstrated a statistically significant reduction in SBP and DBP. Based on the available evidence, the lowest effective dose is 5 mg/day. It is possible the lowest effective dose may be lower than 5 mg/day but there are no available data. Indirect comparisons showed a statistically significant difference in effect sizes between the 10 and 20 mg/day doses.

There was statistically significant heterogeneity in the effect estimate of DBP in the 10 mg/day group ($Chi^2$ = 23.73, p = 0.001, $I^2$ = 70.5%) as well as the SBP effect

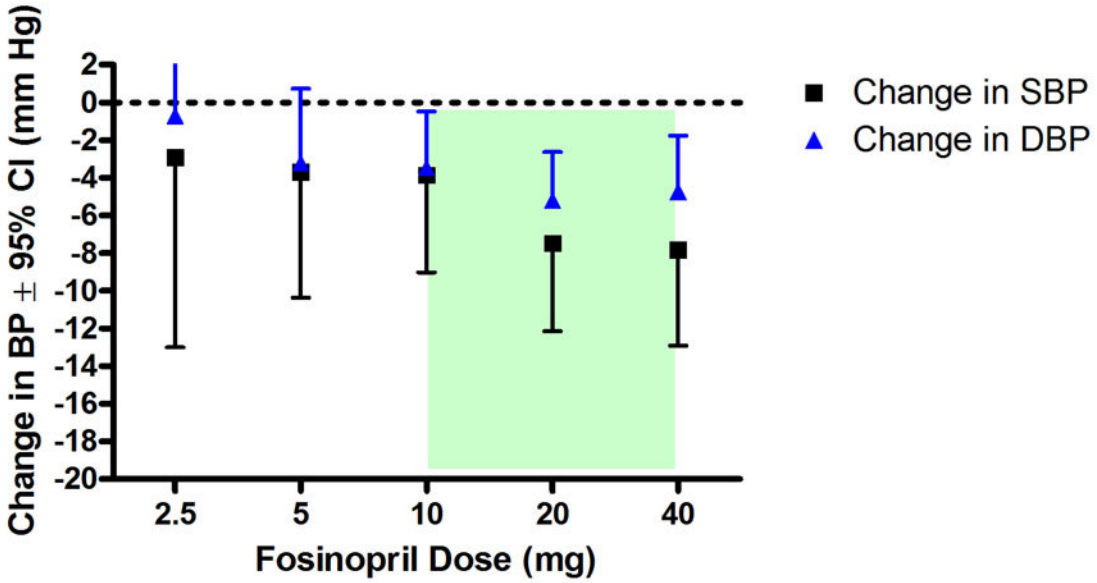
estimate at 20 mg/day ($Chi^2$ = 17.34, p = 0.02, $I^2$ = 59.6%). The random effects model still demonstrated a statistically significant difference from placebo for both groups. The heterogeneity in the two groups can be partly explained by two trials [100,103] that report large reductions in blood pressure with enalapril (-14.10/-7.60 mm Hg for 10 mg/day group in Kuppers 1997 [100]; -20.70/-9.60 mm Hg for 20 mg/day group in Prichard 2002 [103]). Both studies were funded by the same company and used enalapril as an active comparator against their centrally acting antihypertensive drug, moxonidine. When these trials are removed from the analysis, the heterogeneity at 20 mg/day is no longer statistically significant and the SBP effect size is reduced from -9.61 (95% CI -11.35, -7.86) mm Hg to -8.66 (95% CI -10.48, -6.84) mm Hg. The heterogeneity in the 10 mg/day dose for DBP is reduced but is still statistically significant ($Chi^2$ = 14.42, p = 0.03, $I^2$ = 58.4%) and a random effects model still yielded a significant reduction in DBP for 10 mg/day compared with placebo. The remaining heterogeneity is explained by Waeber et al. (1999), which contributes 66% by weight to the estimate of the DBP lowering efficacy at 10 mg/day with enalapril [109]. This trial was designed to compare a fixed dose felodipine-metoprolol combination with the active comparator enalapril as well as placebo; 318 patients were randomized to enalapril 10 mg/day and 300 patients to placebo. Waeber et al. (1999) reported a SBP reduction of -3.80 (95% CI -5.76, -1.84) and DBP reduction of -1.60 (95% CI -2.75, -0.45) compared with placebo.

From the data that are available, it appears that the lowest dose with near maximal blood pressure lowering efficacy is 20 mg/day. Further increases in blood pressure may be achieved at doses higher than 20 mg/day but there are no available data. The best estimate of the near maximal blood pressure lowering efficacy of enalapril at 20 mg/day is -8.66 (95% CI -10.48, -6.84) mm Hg for SBP and -4.80 (95% CI -5.81, -3.79) mm Hg for DBP.

#### 2.2.4.5 Dose-ranging BP lowering efficacy of fosinopril

Six of the included trials evaluated fosinopril from 2.5 to 40 mg/day but there were few studies at each dose and therefore insufficient data to demonstrate a statistically significant difference between any of the doses using indirect comparisons (Figure 2.8).

**Figure 2.8: Log dose-response curve of fosinopril 2.5 - 40 mg/day (Shaded area represents manufacturer's recommended dose range)**




The 2.5 and 5 mg/day groups did not have a statistically significant difference from placebo. The manufacturer's recommended starting dose of 10 mg/day significantly reduced DBP, but not SBP, as compared to placebo. The lowest effective dose appears to be between 10 and 20 mg/day. Compared with placebo, the 20 and 40 mg/day groups had a statistically significant reduction in SBP and DBP.

The best estimate of the lowest dose at which near maximal blood pressure lowering efficacy occurs is 20 mg/day (-9.26/-7.79 mm Hg). However, there was statistically significant heterogeneity in this group. Zamboulis et al. (1996) accounted for the heterogeneity in the 20 mg/day effect estimate because of its remarkably large reduction in blood pressure (-26.40/-19.60 mm Hg) [117]. This small trial did not report the time of the blood pressure measurement. The baseline blood pressure differed between the treatment and placebo groups by 8 mm Hg for SBP and 13 mm Hg for DBP, which brings into question the quality of randomization in this trial. Furthermore, the baseline DBP in the benazepril group was 108 mm Hg whereas the weighted mean DBP in the other trials was 100 mm Hg. Thus, Zamboulis et al. (1996) has been excluded from this analysis. Removal of this trial eliminated the heterogeneity and reduced the change in SBP to -7.46 (95% CI -12.15, -2.77) mm Hg and the change in DBP to -5.20 (95% CI -

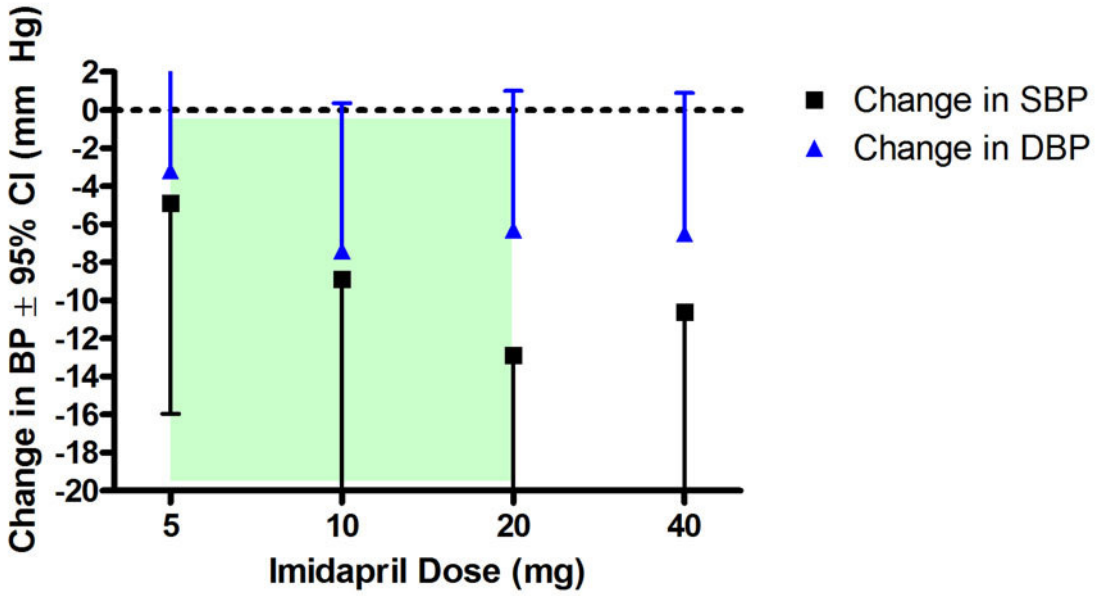
7.77, -2.63) mm Hg.

Based on the available data, the best estimate of the near maximal blood pressure lowering occurs at doses of 20 mg/day and above and has a magnitude of -7.62 (95% CI -11.07, -4.17) mm Hg for SBP and -5.00 (95% CI -6.94, -3.05) mm Hg for DBP.

#### 2.2.4.6 Dose-ranging BP lowering efficacy of imidapril

Only one included multi-arm trial assessed imidapril at doses of 5, 10, 20 and 40 mg/day [118]. Compared with placebo, there was no statistically significant difference in change in DBP for any of the doses studied (Figure 2.9).

**Figure 2.9: Log dose-response curve of imidapril 5 - 40 mg/day (Shaded area represents manufacturer's recommended dose range)**




Only the 20 mg/day group had a significantly greater reduction in SBP compared with placebo. When all doses were combined to establish an overall effect with imidapril, there was a statistically significant reduction in SBP and DBP compared with placebo.

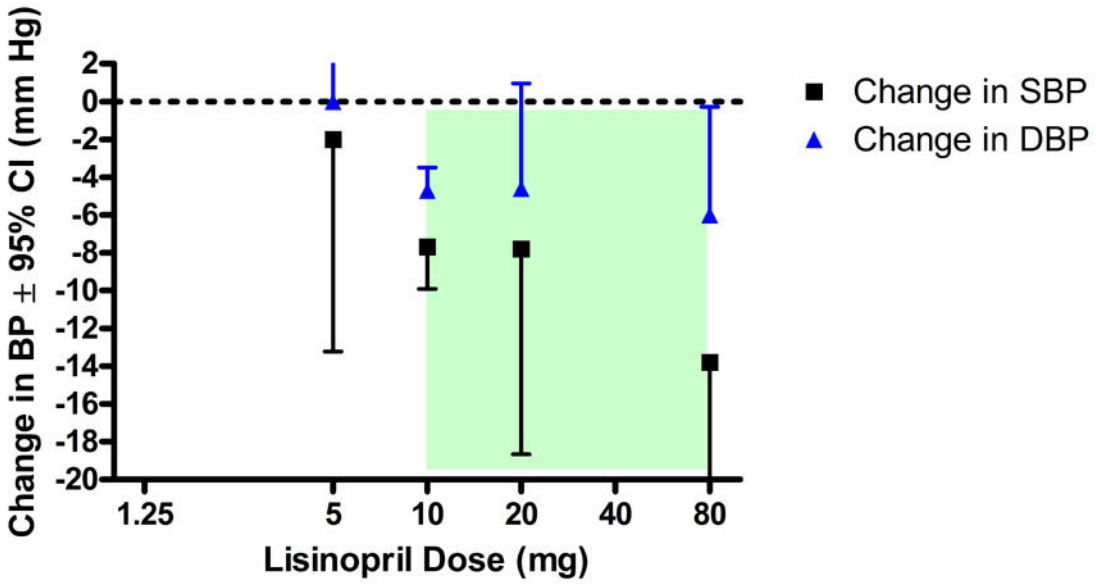
Due to a lack of data for each dose, a dose-response relationship with imidapril could not be statistically established. A visual inspection of the log dose-response curve (Figure 2.9) indicates that the blood pressure lowering efficacy is near maximal at 10 mg/day with a magnitude of -8.90 (95% CI -20.02, 2.22) mm Hg for SBP and -7.40 (95% CI -15.16, 0.36) mm Hg for DBP.

Based on the results of this one trial, the best estimate of the near maximal blood pressure lowering efficacy for imidapril 10 to 40 mg/day is -9.30 (95% CI -14.83, -3.78) mm Hg and -5.76 (95% CI -9.44, -2.07) mm Hg for SBP and DBP, respectively.

### 2.2.4.7 Dose-ranging BP lowering efficacy of lisinopril

Although it appears in Figure 2.10 that lisinopril has been studied over a wide dosage range (1.25 - 80 mg/day), 4 of the 5 included studies assessed lisinopril at 10 mg/day only, while only one small trial investigated lisinopril at all other doses [122]. None of the included trials assessed the blood pressure lowering efficacy at the manufacturer's recommended maintenance dosage of 40 mg/day.

**Figure 2.10: Log dose-response curve of lisinopril 1.25 - 80 mg/day (Shaded area represents manufacturer's recommended dose range)**




Only the 10 and 80 mg/day groups significantly decreased blood pressure compared with placebo. There are insufficient data below 10 mg/day to determine whether or not there is a lower effective dose and 10 mg/day does appear to be the lowest dose with near maximal blood pressure lowering.

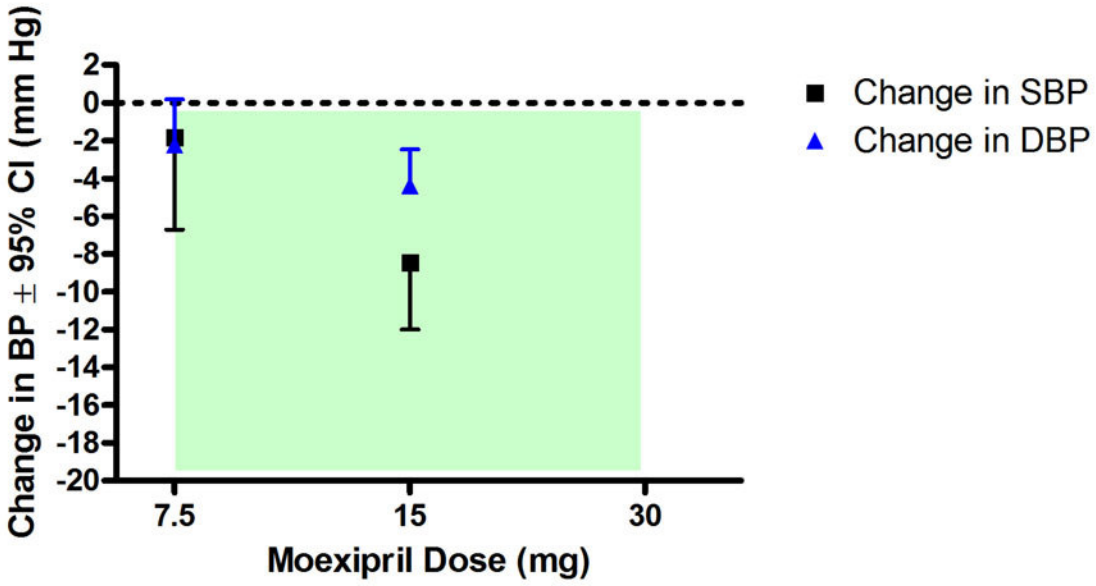
Indirect comparisons showed that there was no statistically significant difference between the effect sizes of 20 and 80 mg/day doses compared with the 10 mg/day dose. Based on the available evidence, the near maximal blood pressure lowering efficacy of

lisinopril for doses 10 to 80 mg/day is -8.00 (95% CI -10.14, -5.85) mm Hg for SBP and -4.76 (95% CI -5.92, -3.60) mm Hg for DBP.

### 2.2.4.8 Dose-ranging BP lowering efficacy of moexipril

Four of the included trials assessed moexipril at 7.5 and 15 mg/day (Figure 2.11). Compared with placebo, only the 15 mg/day group had a statistically significant reduction in blood pressure. An estimate of the near maximal blood pressure lowering efficacy cannot be determined because there were no data for doses above 15 mg/day, including the manufacturer's maximum recommended dose of 30 mg/day.

**Figure 2.11: Log dose-response curve of moexipril 7.5 - 30 mg/day (Shaded area represents manufacturer's recommended dose range)**



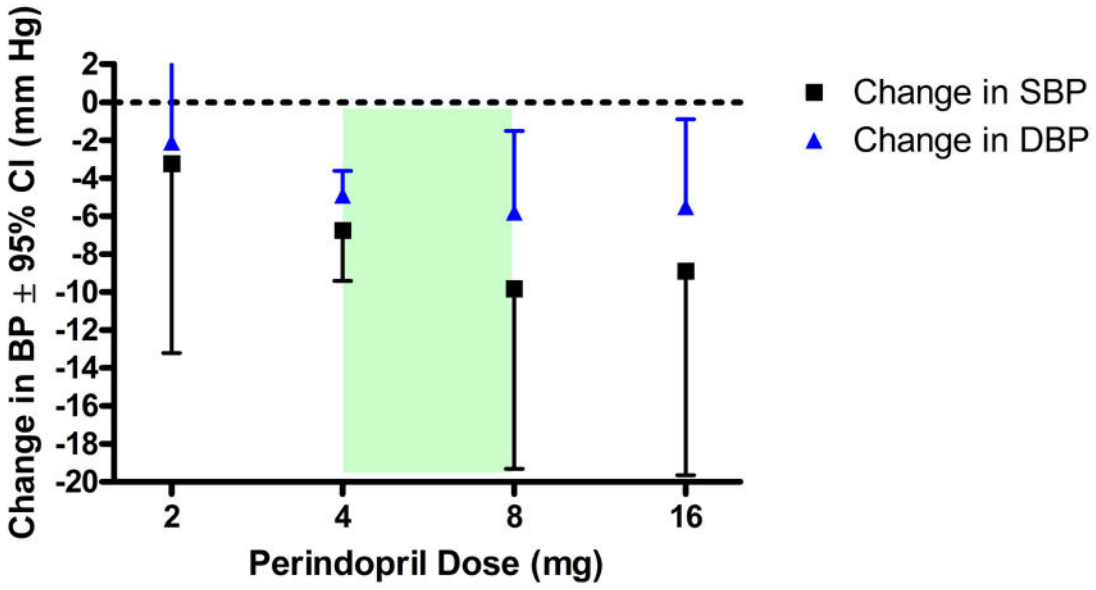

The lowest effective dose is 15 mg/day and, based on the available data, blood pressure lowering at this dosage has a magnitude of -8.45 (95% CI -11.99, -4.91) mm Hg for SBP and -4.38 (95% CI -6.29, -2.46) mm Hg for DBP.

### 2.2.4.9 Dose-ranging BP lowering efficacy of perindopril

Six of the included trials assessed perindopril at a dose range of 2 to 16 mg/day (Figure 2.12). All 6 trials studied perindopril at 4 mg/day, the manufacturer's recommended starting dose, but there was limited trial evidence at the other doses. Only 2 trials provided data at 2 and 8 mg/day [129,130], and one trial assessed perindopril at

16 mg/day [130].

**Figure 2.12: Log dose-response curve of perindopril 2 - 16 mg/day (Shaded area represents manufacturer's recommended dose range)**



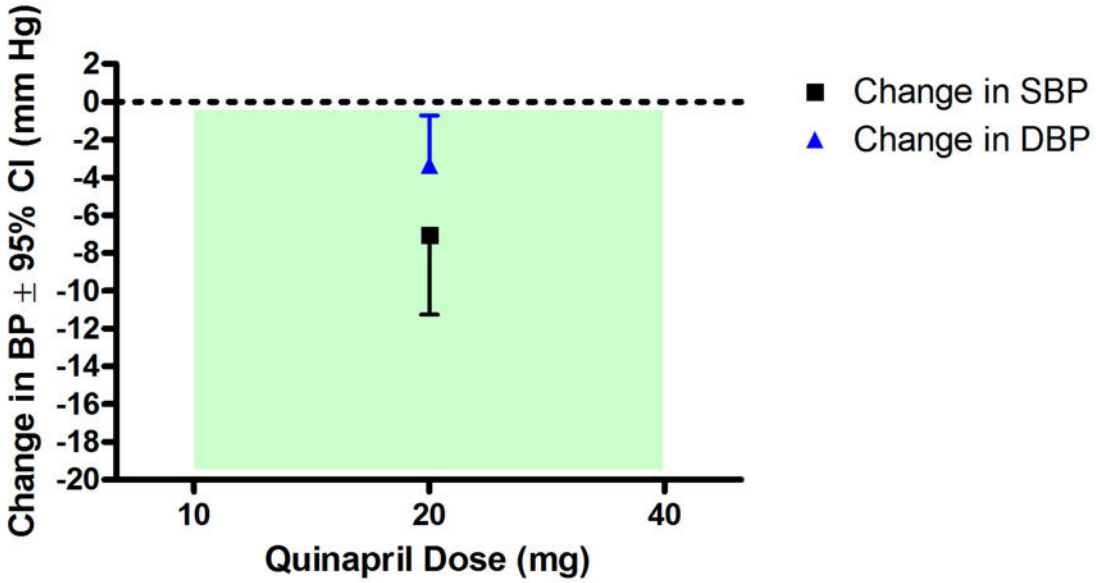

Perindopril 2 mg/day did not demonstrate a statistically significant reduction in blood pressure compared with placebo. The lowest effective dose is 4 mg/day. Due to the wide confidence intervals for the 8 and 16 mg/day doses, indirect comparisons with 4 mg/day did not show a statistically significant difference. Because of the lack of data above and below 4 mg/day, there is very limited information regarding the dose-response of perindopril.

Based on the available data, the best estimate of the near maximal blood pressure lowering efficacy for perindopril 4 to 16 mg/day is -7.09 (95% CI -9.56, -4.61) mm Hg for SBP and -5.02 (95% CI -6.22, -3.82) mm Hg for DBP.

### 2.2.4.10 Dose-ranging BP lowering efficacy of quinapril

Two of the included trials assessed the blood pressure lowering efficacy of quinapril at 20 mg/day (Figure 2.13).

**Figure 2.13: Log dose-response curve of quinapril 10 - 40 mg/day (Shaded area represents manufacturer's recommended dose range)**

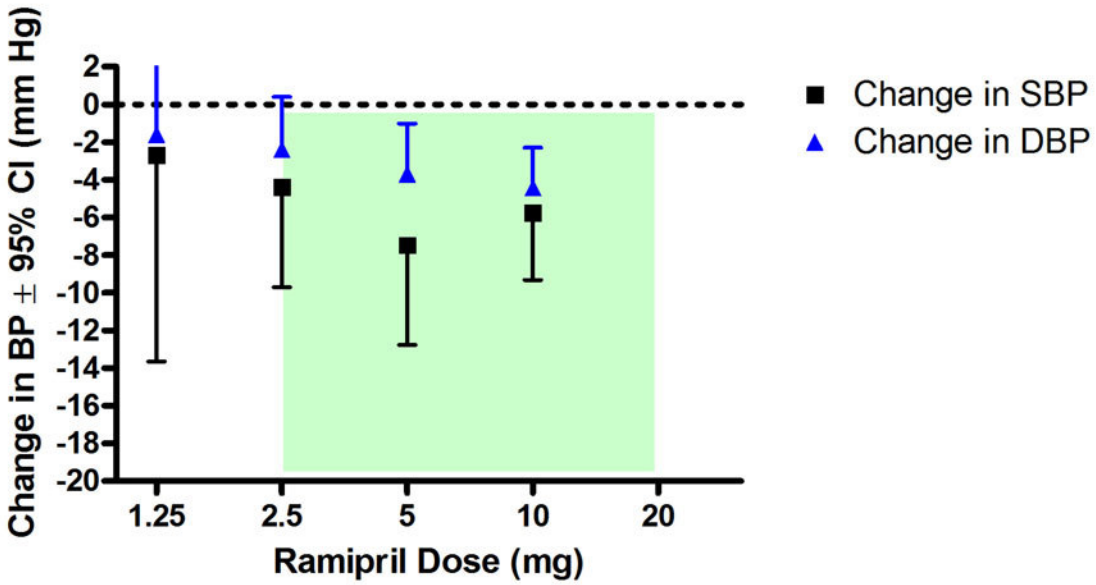



There were no data available for 10 and 40 mg/day, the manufacturer's recommended starting and maximum dose, respectively. At 20 mg/day, quinapril had a statistically significant reduction in blood pressure compared with placebo. However, it cannot be established if the lowest effective dose is 20 mg/day. Furthermore, because there were no data for doses above 20 mg/day, the near maximal blood pressure lowering efficacy cannot be estimated. The magnitude of the blood pressure lowering efficacy of quinapril at 20 mg/day is -7.05 (95% CI -11.26, -2.84) mm Hg for SBP and -3.35 (95% CI -5.98, -0.72) mm Hg for DBP.

### 2.2.4.11 Dose-ranging BP lowering efficacy of ramipril

Six of the included studies assessed ramipril at doses ranging from 1.25 to 10 mg/day (Figure 2.14).

**Figure 2.14: Log dose-response curve of ramipril 1.25 - 20 mg/day (Shaded area represents manufacturer's recommended dose range)**



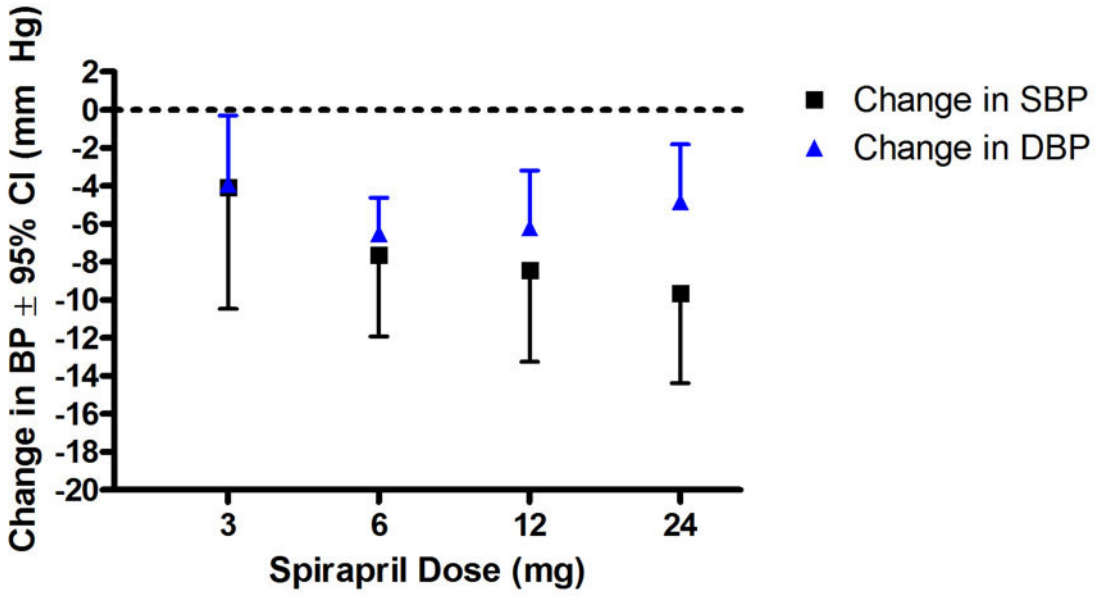

Compared with placebo, the manufacturer's recommended starting dose did not significantly reduce blood pressure. A significant decrease in SBP and DBP was seen at 5 and 10 mg/day but there was no statistically significant difference between the two doses based on an indirect comparison. No included trials assessed the manufacturer's maximum recommended dose of 20 mg/day.

The lowest effective dose is 5 mg/day. Due to a lack of data, it cannot be determined if doses above 10 mg/day have greater efficacy. Thus, an estimate of the near maximal blood pressure lowering efficacy of ramipril cannot be made. Based on the results of the two doses that were effective, the best estimate of the blood pressure lowering effect of ramipril at 5 to 10 mg/day is -6.29 (95% CI -9,26, -3.32) mm Hg for SBP and -4.14 (95% CI -5.81, -2.48) mm Hg for DBP.

### 2.2.4.12 Dose-ranging BP lowering efficacy of spirapril

The patent for spirapril expired in 2003 and it is no longer marketed in North America. The recommended starting dose and the maximum daily dose for the treatment of primary hypertension could not be found, explaining the lack of a shaded region in Figure 2.15.

**Figure 2.15: Log dose-response curve of spirapril 3 - 24 mg/day**



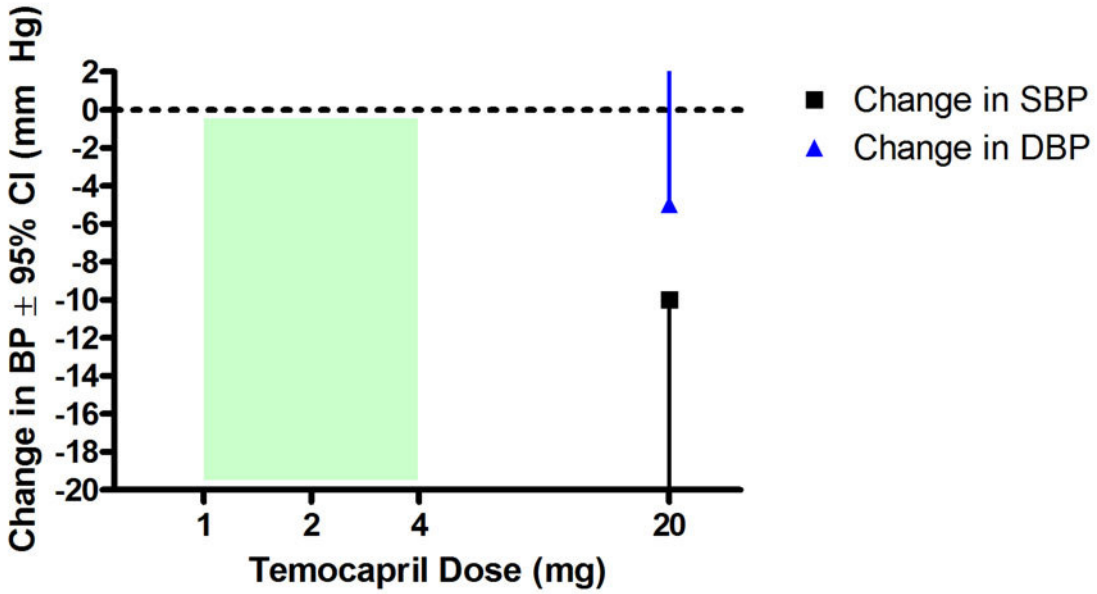

All doses significantly reduced blood pressure compared with placebo except for change in SBP at 3 mg/day. The lowest effective dose appears to be between 3 and 6 mg/day. For SBP and DBP, there was no statistically significant difference in effect sizes between 6 and 24 mg/day using indirect comparisons. Thus, the estimate of the lowest dose at which near maximal blood pressure lowering occurs is 6 mg/day. The best estimate of the near maximal blood pressure lowering efficacy for spirapril is -8.54 (95% CI -11.18, -5.89) mm Hg and -6.08 (95% CI -7.50, -4.66) mm Hg for SBP and DBP, respectively.

### 2.2.4.13 Dose-ranging BP lowering efficacy of temocapril

There were no included trials that assessed the blood pressure lowering efficacy of temocapril within the manufacturer's recommended dose range of 1 to 4 mg/day

(Figure 2.16).

**Figure 2.16: Log dose-response curve of temocapril 1 - 20 mg/day (Shaded area represents manufacturer's recommended dose range)**

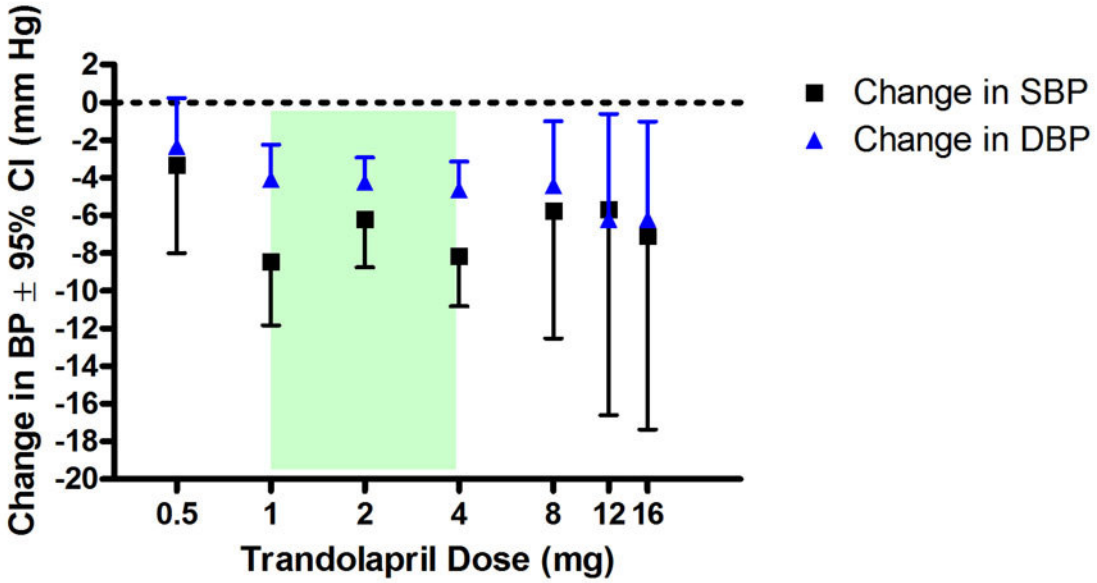



One included trial assessed temocapril at 20 mg/day [149]. The 20 mg/day dose did not show a statistically significant difference compared with placebo but, as indicated by the extremely wide confidence intervals, this is likely due to the lack of data at this dose.

#### 2.2.4.14 Dose-ranging BP lowering efficacy of trandolapril

All doses of trandolapril above 0.5 mg/day resulted in a statistically significant reduction in blood pressure compared with placebo (Figure 2.17).

**Figure 2.17: Log dose-response curve of trandolapril 0.5 - 16 mg/day (Shaded area represents manufacturer's recommended dose range)**




The manufacturer's recommended starting dose of 1 mg/day is the lowest effective dose that showed a statistically significant difference from 0.5 mg/day. Indirect comparisons showed that increasing the daily dose beyond 1 mg/day does not significantly reduce blood pressure further.

Two trandolapril trials assessed the blood pressure lowering efficacy of 8 mg/day in black patients [151,164], and only one trial assessed black patients after treatment with trandolapril at 0.5, 12 and 16 mg/day [164]. However, very few black patients were studied at these doses to statistically assess whether there is a difference in efficacy between black and non-black patients.

The lowest dose with near maximal blood pressure lowering efficacy is 1 mg/day. Based on the available trial evidence, the best estimate of the near maximal blood pressure lowering efficacy of trandolapril for doses of 1 to 16 mg/day is -7.31 (95% CI -8.85, -5.77) mm Hg for SBP and -4.42 (95% CI -5.24, -3.60) mm Hg for DBP.

### 2.2.5 Summary of the BP lowering efficacy of ACE inhibitors

Table 2.17 provides an overview of the lowest effective dose, the lowest dose with near maximal blood pressure lowering and the near maximal blood pressure lowering effect of each ACE inhibitor studied in this review.

**Table 2.17: Summary of the BP lowering efficacy of ACE inhibitors**

| ACE Inhibitor | Lowest effective dose (mg/day) | Lowest dose with near maximal BP lowering (mg/day) | Near maximal trough SBP lowering (mm Hg), 95% CI | Near maximal trough DBP lowering (mm Hg), 95% CI |
|---|---|---|---|---|
| benazepril | 20 | 20 | -8.70 (-11.43, -5.97) | -4.92 (-6.47, -3.36) |
| captopril | 37.5 | 37.5 | -9.68 (-11.73, -7.63) | -5.43 (-6.47, -4.40) |
| cilazapril | 2.5 | 2.5 | -5.58 (-7.84, -3.32) | -3.50 (-4.40, -2.60) |
| enalapril | 5 | 20 | -8.66 (-10.48, -6.84) | -4.80 (-5.81, -3.79) |
| fosinopril | 10-20 | 20 | -7.62 (-11.07, -4.17) | -5.00 (-6.94, -3.05) |
| imidapril | Not estimable | Not estimable | -9.30 (-14.83, -3.78) | -5.76 (-9.44, -2.07) |
| lisinopril | 10 | 10 | -8.00 (-10.14, -5.85) | -4.76 (-5.92, -3.60) |
| moexipril | 15 | Not estimable | -8.45 (-11.99, -4.91) | -4.38 (-6.29, -2.46) |
| perindopril | 4 | 4 | -7.09 (-9.56, -4.61) | -5.02 (-6.22, -3.82) |
| quinapril | Not estimable | Not estimable | -7.05 (-11.26, -2.84) | -3.35 (-5.98, -0.72) |
| ramipril | 5 | 5 | -6.29 (-9.26, -3.32) | -4.14 (-5.81, -2.48) |
| spirapril | 3-6 | 6 | -8.54 (-11.18, -5.89) | -6.08( -7.50, -4.66) |
| temocapril | Not estimable | Not estimable | -10.00 (-23.87, 3.87) | -5.00 (-13.34, 3.34) |
| trandolapril | 1 | 1 | -7.31 (-8.85, -5.77) | -4.42 (-5.24, -3.60) |

The lowest effective dose is defined as the lowest dose for which there is a statistically significant difference from placebo. The lowest dose with near maximal blood pressure lowering efficacy is defined as the dose that demonstrates a statistically significantly greater response than doses below it, but does not exhibit a statistically significant difference in effect size compared with higher doses. If there was any discrepancy between SBP and DBP, SBP was used to define the doses.

ACE inhibitors were analyzed as a class by pooling all trials reporting trough blood pressure and categorizing individual doses as proportions of the manufacturer's maximum recommended daily dose (Max). The pooled efficacy data ranged from 1/16 Max to 2 Max (Figures 2.18 - 2.23).

**Figure 2.18: BP lowering efficacy of ACE inhibitors at 1/16 Max**

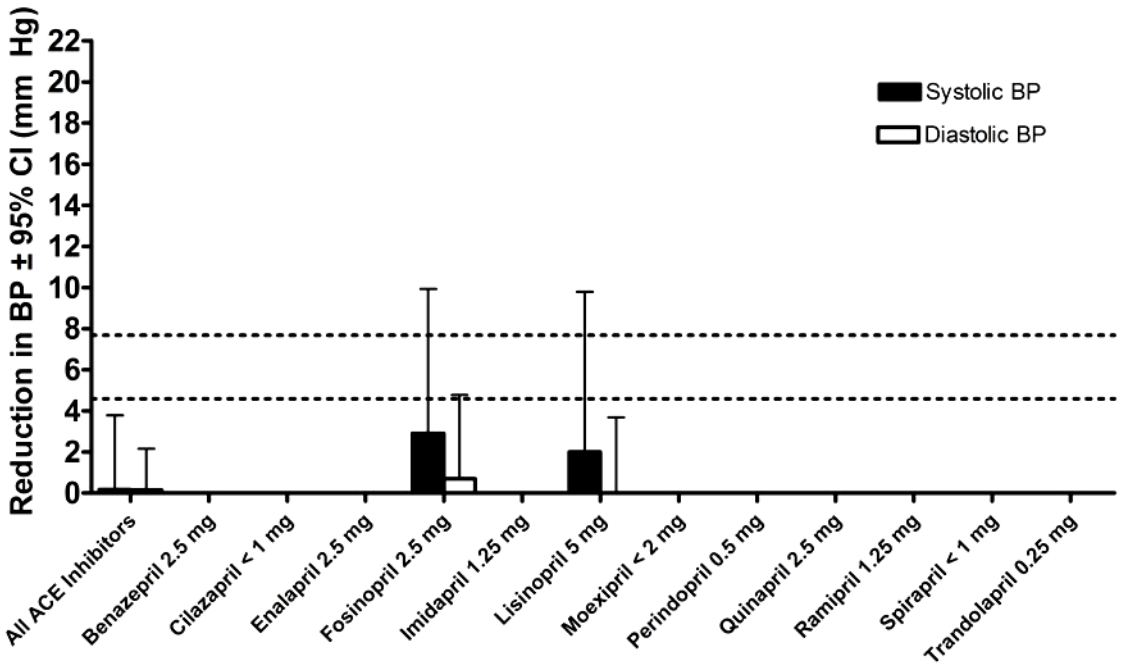



**Figure 2.19: BP lowering efficacy of ACE inhibitors at 1/8 Max**

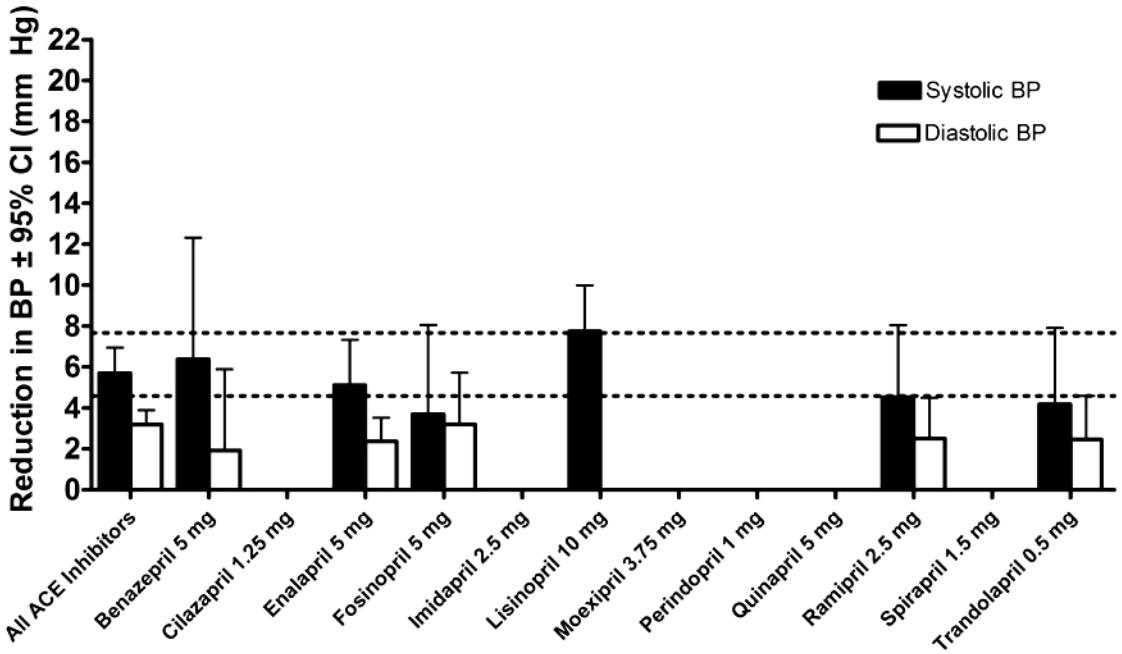


**Figure 2.20: BP lowering efficacy of ACE inhibitors at 1/4 Max**

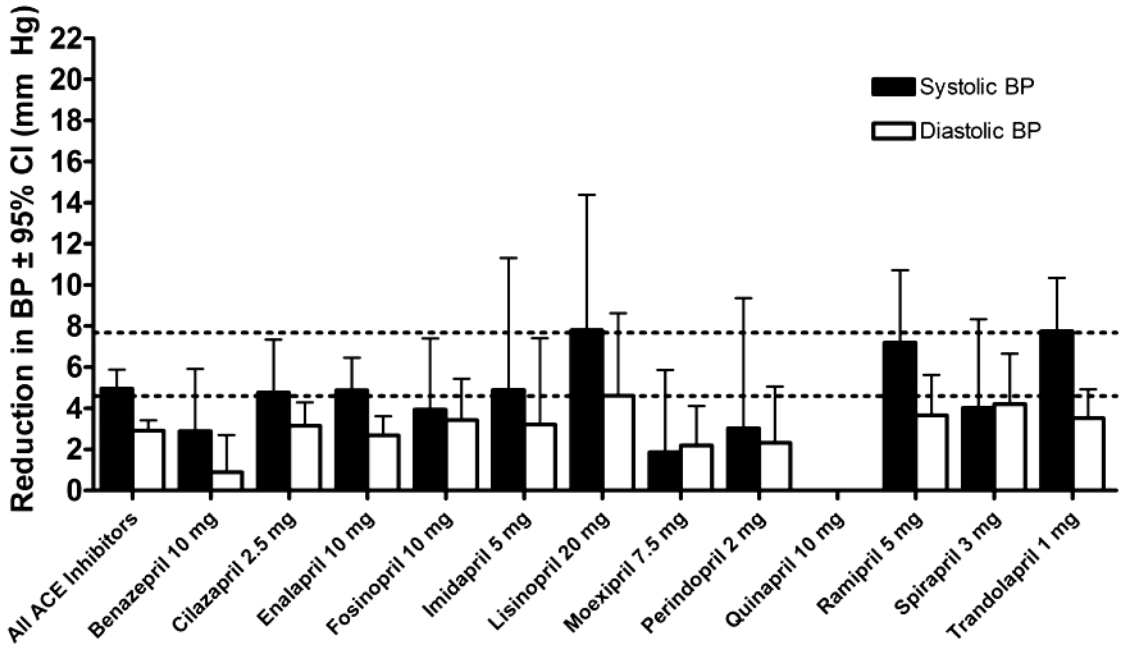



**Figure 2.21: BP lowering efficacy of ACE inhibitors at 1/2 Max**

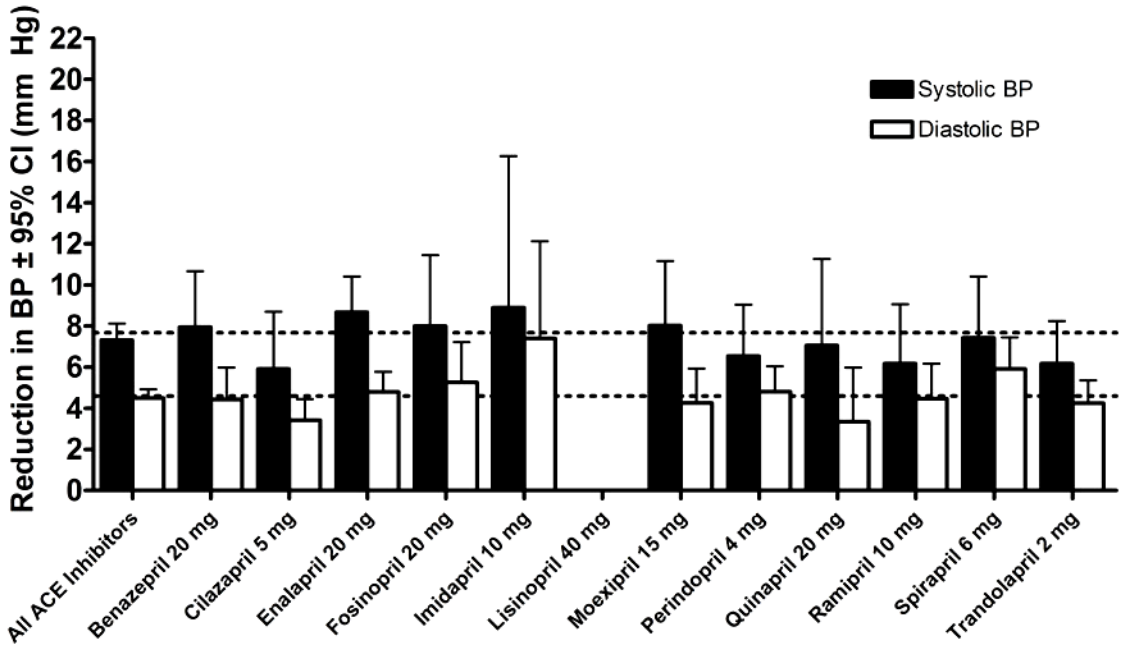


**Figure 2.22: BP lowering efficacy of ACE inhibitors at Max**

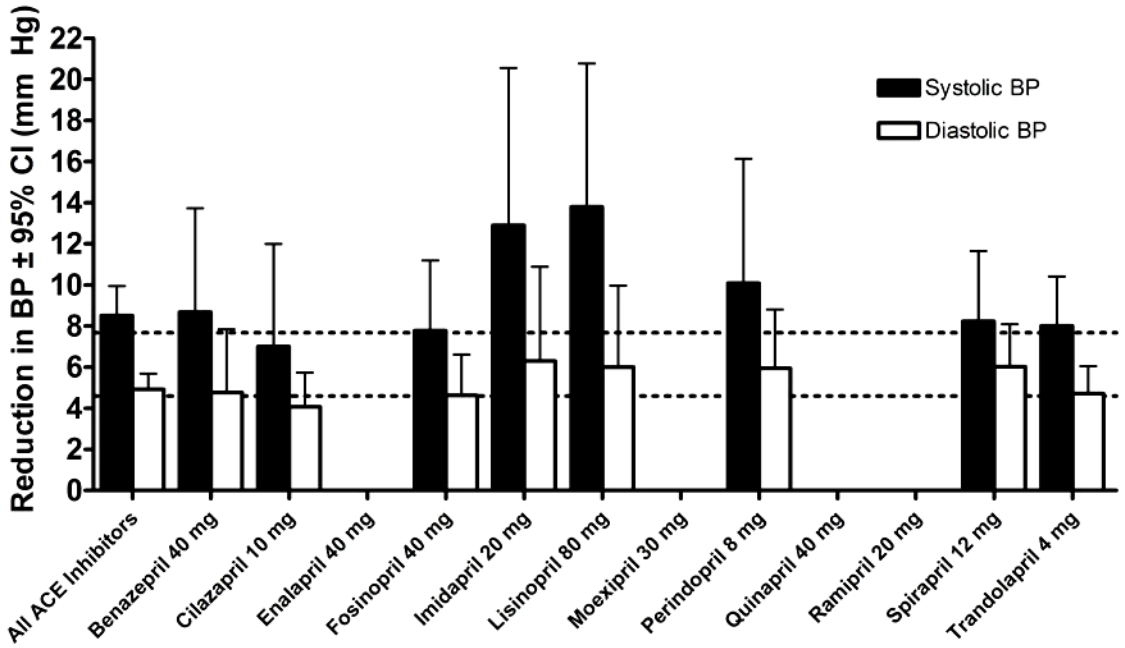
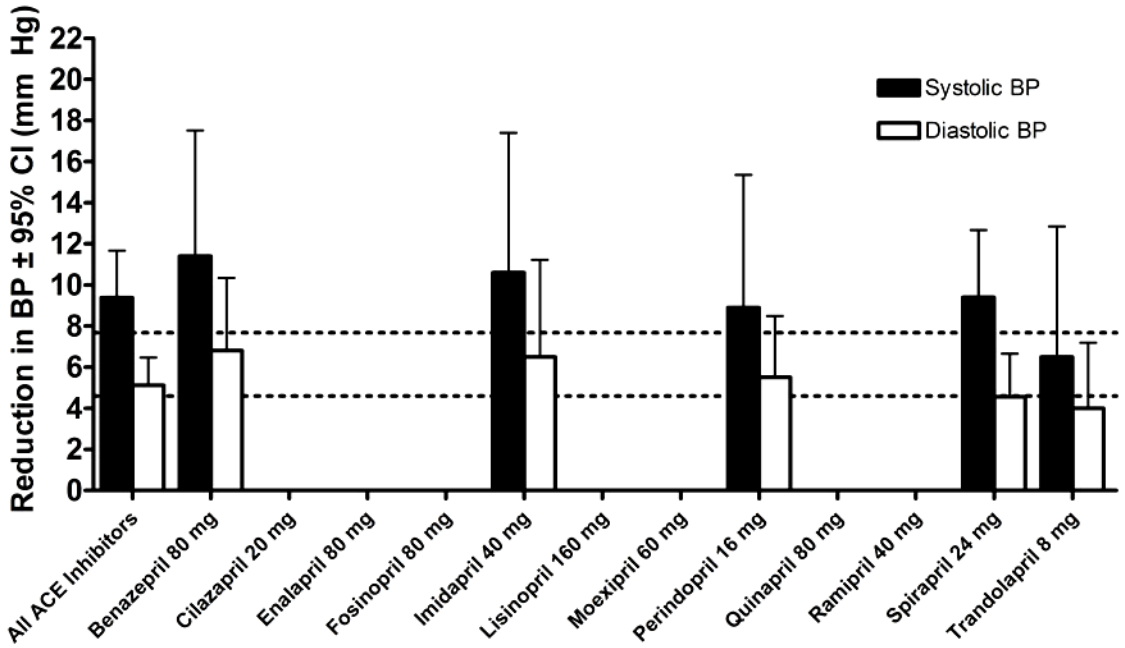


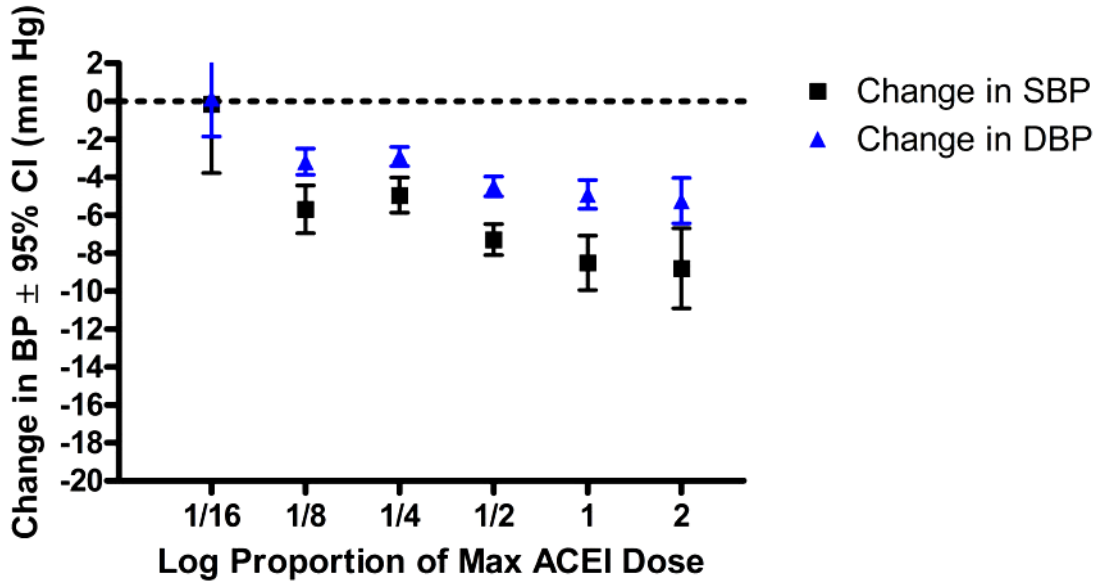

**Figure 2.23: BP lowering efficacy of ACE inhibitors at 2 Max**




The pooled efficacy data were evaluated for the presence of a dose-response relationship. As shown in Figure 2.24, a dose-response is present with a statistically significant difference between 1/4 Max and 1/2 Max. Further increases in the dosage

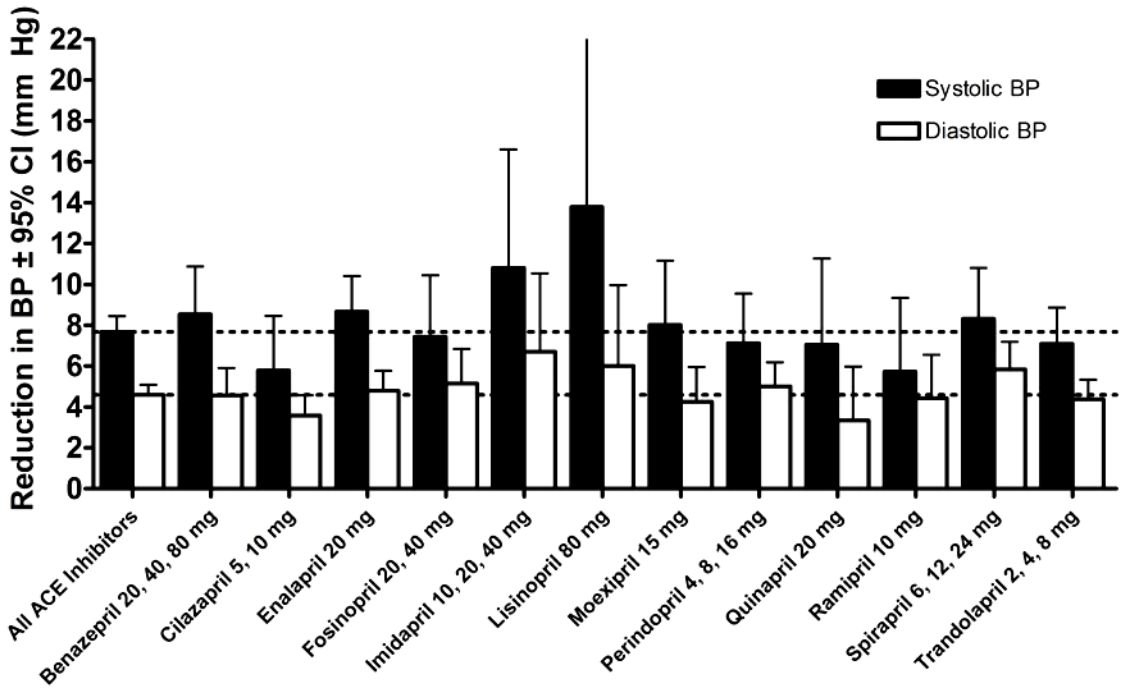
beyond 1/2 Max did not result in a statistically significantly greater reduction in blood pressure.

**Figure 2.24: Log dose-response curve of ACE inhibitors according to proportions of Max**




Thus, near maximal blood pressure lowering is achieved at half of the manufacturers' recommended maximum dose and above (Figure 2.25). Using this definition, the best estimate of the near maximal blood pressure lowering efficacy for the ACE inhibitor class of drugs is -7.68 (95% CI -8.45, -6.91) mm Hg for SBP and -4.59 (95% CI -4.99, -4.19) mm Hg for DBP.

**Figure 2.25: Near maximal BP lowering efficacy of ACE inhibitors**




### 2.2.6 Analysis of publication bias

#### 2.2.6.1 Funnel plots

In order to test for the possibility of publication bias in the ACE inhibitor review, funnel plots were created of the trough SBP (Figure 2.26) and DBP (Figure 2.27) lowering effects of all doses of 1/2 Max and higher. These plots were reasonably symmetrical and there did not appear to be a paucity of smaller trials with small or absent blood pressure lowering effect.

**Figure 2.26: Funnel plot of near maximal change in trough SBP for ACE inhibitors at 1/2 Max and higher doses**

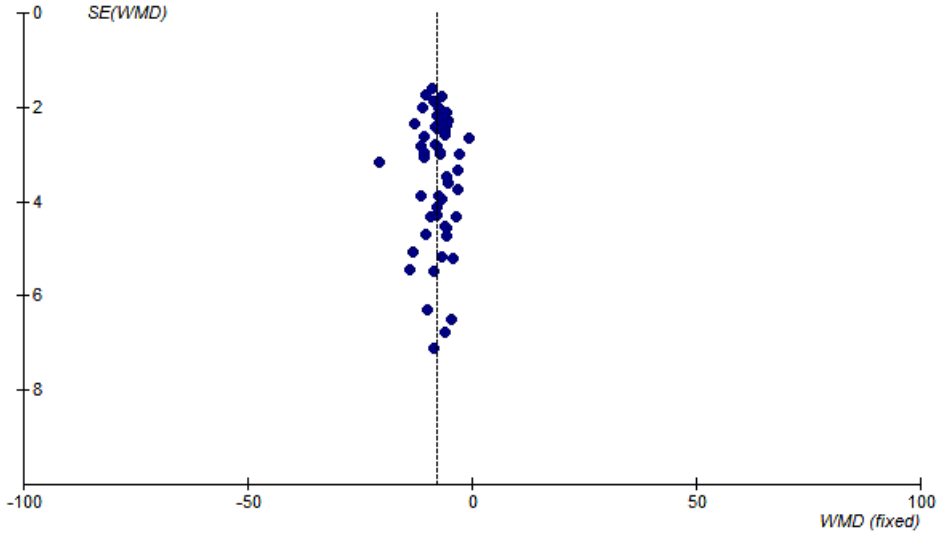
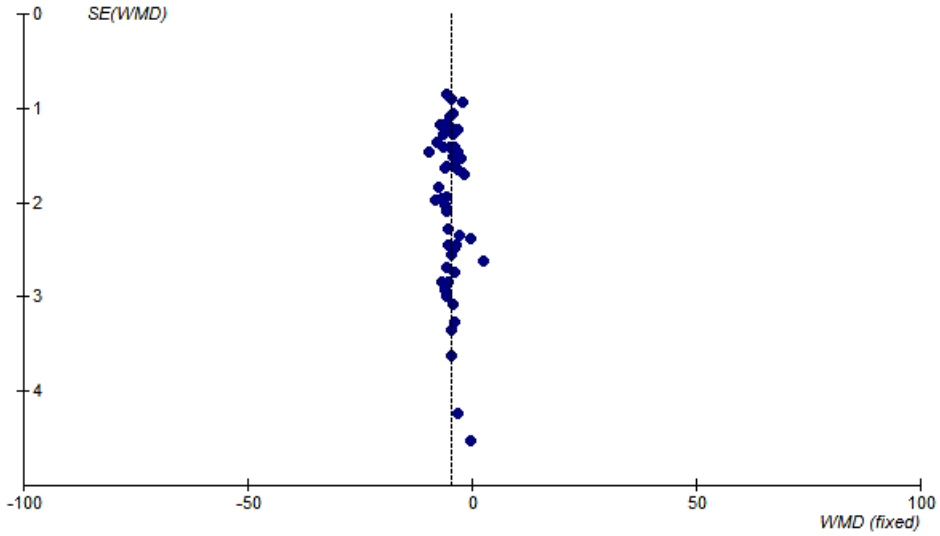



**Figure 2.27: Funnel plot of near maximal change in trough DBP for ACE inhibitors at 1/2 Max and higher doses**



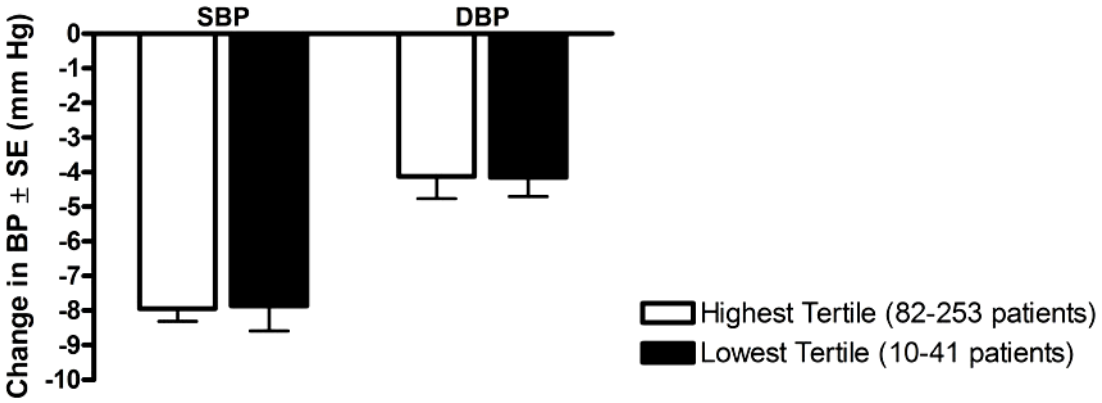

### 2.2.6.2 Tertile analysis based on trial size

To further test for possible publication bias, a post-hoc tertile analysis was performed to determine if the magnitude of blood pressure lowering differed according to trial size. Once again, all ACE inhibitor doses of 1/2 Max and above were divided into tertiles according to the sample size in the active treatment arms. The lowest, middle and

highest tertiles represented the smallest, medium-sized and largest trials, respectively. The mean effect size of the largest trials (highest tertile) was compared with that of the smallest trials (lowest tertile) using an unpaired t test (the indirect method).

As shown in Figure 2.28, this tertile analysis did not suggest the presence of publication bias in the ACE inhibitor systematic review; there were no statistically significant differences in effect size between the largest (n=82-253 patients) and smallest (n=10-41 patients) trials for both SBP (p=0.9) and DBP (p=1.0).

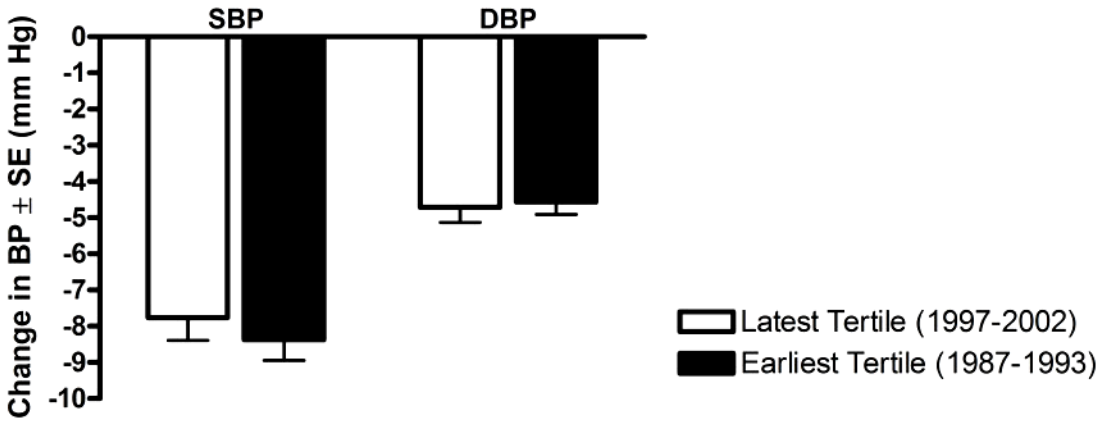
**Figure 2.28: Post-hoc tertile analysis of the effect of trial size on reported trough BP lowering**




### 2.2.6.3 Tertile analysis based on publication year

Another possible source of bias in the ACE inhibitor review is bias introduced because the patients chosen for the trial were already known to respond well to ACE inhibitors. If this were occurring, it was hypothesized that there would be little possibility for this to happen in the earliest published trials and that it would be more likely to occur in later published trials when use of the class was more common. A post-hoc tertile analysis was done to determine the effect of the year of publication of trials on the blood pressure lowering effect. This analysis was done for all ACE inhibitor doses at 1/2 Max and above (Figure 2.29). The mean effect size of the latest tertile (1997-2002) was compared with that of the earliest tertile (1987-1993) using the indirect method and there was no statistically significant difference for SBP (p=0.5) or DBP (p=0.8) between the tertiles.

**Figure 2.29: Post-hoc tertile analysis of the effect of publication year on reported trough BP lowering**




### 2.2.7 Blood pressure variability

The variability of blood pressure at both baseline and endpoint was reported for 26 (28%) of the included trials. In Table 2.18, the number of observations represents the number of active treatment arms in these 26 trials.

**Table 2.18: Variability of systolic and diastolic BP at end of treatment**

| | | ACE Inhibitor | Placebo |
|---|---|---|---|
| SBP | Weighted mean SD | 16.6 | 16.8 |
| | SD of weighted mean SD | 3.1 | 3.0 |
| | Weighted mean SBP | 146.0 | 152.9 |
| | Weighted mean coefficient of variation (CV) | 11.2 | 11.0 |
| | SD of weighted mean CV | 2.1 | 2.0 |
| | Number of observations | 22 | 19 |
| DBP | Weighted mean SD | 9.0 | 8.9 |
| | SD of weighted mean SD | 1.7 | 1.8 |
| | Weighted mean DBP | 91.8 | 96.4 |
| | Weighted mean CV | 9.8 | 9.2 |
| | SD of weighted mean CV | 1.8 | 1.9 |
| | Number of observations | 20 | 18 |
| t-test | SD of SBP vs. SD of DBP | $p < 0.0001$ | $p < 0.0001$ |
| t-test | CV SBP vs. CV DBP | $p = 0.0227$ | $p = 0.0045$ |

Ninety (98%) of the studies had diastolic hypertension entry criteria, 2 (2.2%) trials had systo-diastolic hypertension entry criteria [69,71], and no trials had isolated systolic hypertension entry criteria.

#### 2.2.7.1 Systolic versus diastolic blood pressure variability

The weighted mean standard deviations for SBP and DBP were compared in order to determine whether SBP varies to the same degree as DBP. For both the ACE inhibitor group and placebo group, the absolute variability of SBP is statistically significantly greater than that of DBP (Table 2.18). The coefficient of variation in SBP was also significantly greater than the coefficient of variation in DBP for both the ACE inhibitor and placebo groups.

#### 2.2.7.2 ACE inhibitors versus placebo

Table 2.18 shows the weighted mean endpoint SD of SBP was 16.6 mm Hg for the ACE inhibitor group and 16.8 mm Hg for the placebo group ($p = 0.8$). The weighted mean SD of DBP was 9.0 mm Hg for the ACE inhibitor group and 8.9 mm Hg for the placebo group ($p = 0.8$). Based on the available evidence, there was no statistically significant difference in the endpoint blood pressure variability between the ACE inhibitor and placebo groups.

#### 2.2.7.3 The effect of blood pressure entry criteria on variability

The included trials were categorized according to blood pressure entry criteria used: 1) diastolic hypertension; 2) systolic hypertension; and 3) systo-diastolic hypertension. None of the included studies had isolated systolic hypertension entry criteria. Only 2 trials had systo-diastolic hypertension entry criteria and therefore a comparison with this subgroup was not feasible [69,71]. To determine the effect of diastolic blood pressure entry criteria on baseline blood pressure variability, the weighted mean baseline standard deviations of these trials were compared.

#### 2.2.7.4 Baseline versus endpoint variability

As shown in Table 2.19, the standard deviations of blood pressure at baseline and endpoint were compared for trials with DBP entry criteria. For the ACE inhibitor group

and placebo group, there was no statistically significant difference between the variability of SBP at baseline and endpoint. DBP variability at endpoint was significantly higher than at baseline in both the ACE inhibitor and placebo groups.

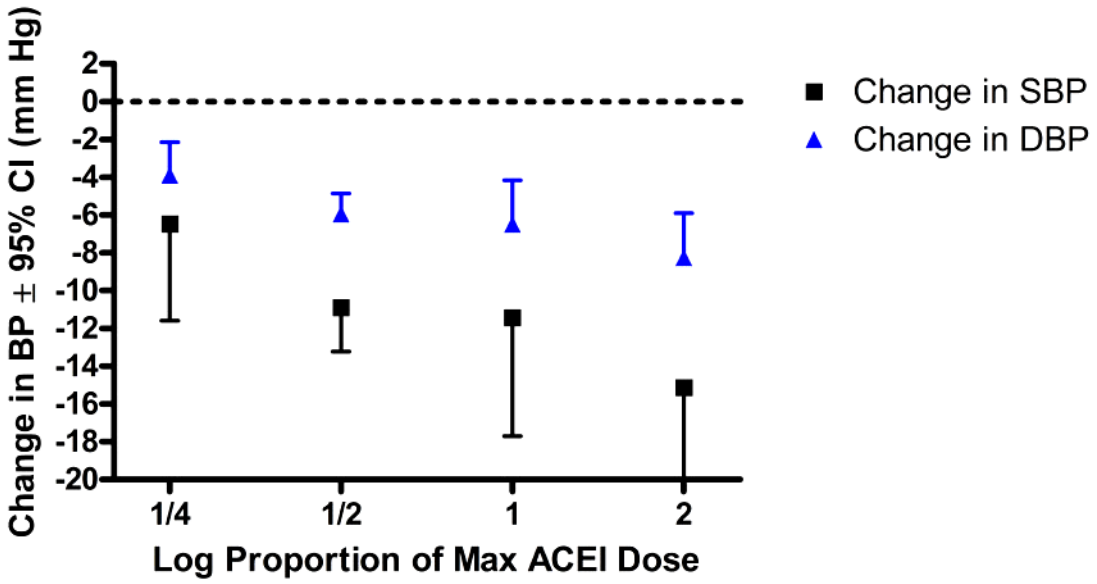
**Table 2.19: Standard deviations of BP at baseline versus endpoint in trials with DBP entry criteria**

| | | ACE Inhibitor | Placebo |
|---|---|---|---|
| Weighted mean SD of SBP | At baseline (SD) | 14.8 (3.0) | 14.9 (2.8) |
| | At endpoint (SD) | 16.6 (3.1) | 16.8 (3.0) |
| t-test | baseline vs. endpoint | p = 0.06 | p = 0.05 |
| Weighted mean SD of DBP | At baseline (SD) | 5.1 (1.5) | 5.1 (1.6) |
| | At endpoint (SD) | 9.0 (1.7) | 8.9 (1.8) |
| t-test | baseline vs. endpoint | p < 0.0001 | p < 0.0001 |

### 2.2.8 Dose-ranging peak blood pressure lowering efficacy

Nine of the included trials reported the peak blood pressure lowering effect of ACE inhibitors. Peak blood pressure data were pooled across trials by categorizing individual doses as proportions of Max, ranging from 1/4 to 2 Max (Figure 2.30).

**Figure 2.30: Log dose-response curve of peak BP lowering efficacy of ACE inhibitors according to proportions of Max**



All doses exhibited a statistically significant reduction in peak SBP and DBP compared with placebo. Indirect comparison analysis of the results for each proportion of Max showed evidence of a dose-response since there was a greater reduction in blood pressure with 2 Max compared with 1/4 Max. There was no statistically significant difference in the effect sizes between 1/2 Max and 2 Max. Pooling the effects of all doses from 1/2 Max to 2 Max provides an estimate of the peak blood pressure lowering effect of ACE inhibitors, -11.43 (95% CI -13.40, -9.45) mm Hg for SBP and -6.35 (95% CI -7.19, -5.50) mm Hg for DBP.

### 2.2.9 Dose-ranging effect on pulse pressure

Pulse pressure was not reported as an outcome in any of the included trials so the change in pulse pressure was calculated by subtracting the change in DBP from the change in SBP for each trial that reported both SBP and DBP. Seventy four (80%) of the included studies provided data to calculate the change in trough pulse pressure. A weighted mean and weighted standard deviation of the change in pulse pressure from baseline was then computed for each proportion of the recommended maximum dose (Table 2.20).

**Table 2.20: Change in pulse pressure according to proportions of Max**

| | Proportion of recommended maximum dose (Max) | Number of studies | Weighted mean change from baseline in pulse pressure (95% CI) |
|---|---|---|---|
| ACE Inhibitor | 1/8 Max | 18 | -1.2 (-2.0, -0.4) |
| | 1/4 Max | 40 | -1.8 (-2.6, -0.9) |
| | 1/2 Max | 50 | -2.5 (-3.2, -1.9) |
| | Max | 16 | -3.7 (-5.5, -1.9) |
| | 2 Max | 6 | -4.1 (-6.3, -1.9) |
| | 1/2 Max and above | 54 | -2.9 (-3.5, -2.3) |
| Placebo | | 74 | 0.6 (0.1, 1.1) |

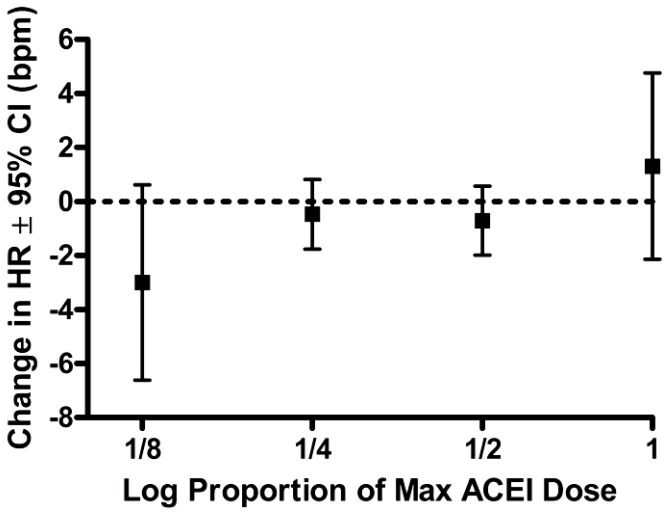
Based on the available evidence, there was a marginal increase from baseline in pulse pressure in patients randomized to placebo. All doses of ACE inhibitors demonstrated statistically significant reductions from baseline in pulse pressure compared with placebo. At 1/2 Max and above, where near maximal blood pressure lowering is achieved, the estimate of the average reduction in pulse pressure was 2.9 and when this

was compared to placebo it became 3.5 (95% CI 2.7, 4.3) mm Hg.

### 2.2.10 Dose-ranging effect on heart rate

Of the 92 included studies, 16 (17%) reported dose-related trough heart rate data. There were few trials to adequately assess the heart rate effect of individual ACE inhibitors. Thus the data were pooled across all trials that reported this outcome and categorized as proportions of the manufacturer's maximum recommended daily dose. Based on the available evidence, there was no statistically significant change in heart rate compared with placebo over the range of 1/8 Max to Max (Figure 2.31).

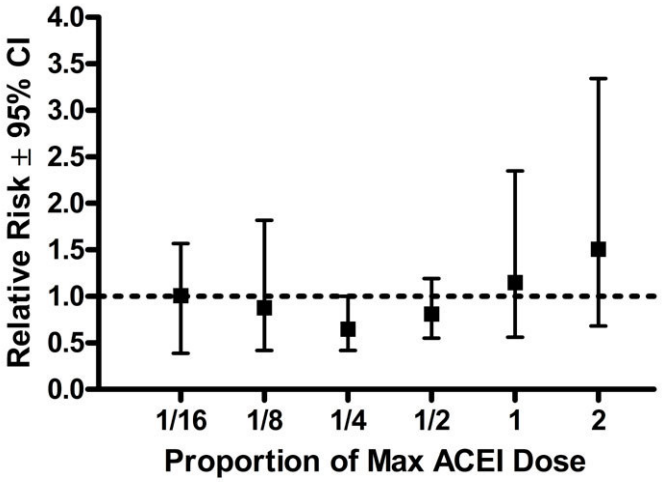
**Figure 2.31: Log dose-response curve assessing the effect of ACE inhibitors on heart rate**




### 2.2.11 Dose-ranging effect on withdrawals due to adverse effects

Fifty five of the included studies (60%) reported dose-related withdrawals due to adverse effects (WDAE) during the 3 to 12 week treatment period. There were not enough data to construct a meaningful dose-response relationship for individual ACE inhibitors. The data are therefore categorized according to the proportions of Max over a dose range of 1/8 Max to Max (Figure 2.32).

**Figure 2.32: Log dose-response curve assessing the effect of ACE inhibitors on withdrawals due to adverse effects**




At 1/4 Max, there was a marginally non-significant [RR 0.65 (95% CI 0.42, 1.00)] reduction in WDAE and there was a trend towards an increased WDAE with higher doses, but none of the doses demonstrated a statistically significant difference compared with placebo. A pooled estimate for all doses resulted in a statistically non-significant relative risk of 0.85 (95% CI 0.67, 1.07). The doses at which near maximal blood pressure lowering efficacy is achieved (1/2 Max and above) also showed no statistically significant difference in WDAE [0.96 (95% CI 0.70, 1.31)] compared with placebo.

## 2.3 Discussion

Ninety two trials with a mean duration of 6 weeks met the pre-specified inclusion criteria and reported data on 12 954 participants (8210 treated with ACE inhibitors and 4744 treated placebo) with a mean age of 54 years, mean baseline blood pressure of 157/101 mm Hg and a mean pulse pressure of 56 mm Hg.

### 2.3.1 Is there a difference in the magnitude of BP lowering effect between individual drugs in the ACE inhibitor class?

This review provides a reasonable amount of data to assess the trough blood pressure lowering effect of 14 different ACE inhibitors. When the different ACE inhibitors are compared, there is a remarkable similarity in their blood pressure lowering effects at trough. When the best estimate of the blood pressure lowering efficacy of these

14 drugs is compared, they range from -6/-4 mm Hg to -9/-5 mm Hg. The data are most consistent with the near maximum blood pressure lowering effect of the each of the drugs being the same. However, for most of the drugs there are insufficient data over a broad dose range. It is therefore impossible with this analysis to be certain that there are no blood pressure lowering differences between one or more of the drugs. It would require head-to-head trials of different ACE inhibitors at equivalent blood pressure lowering doses to assess whether or not there are differences between different drugs. This review will provide useful information for estimating equivalent doses and thereby designing trials to compare different ACE inhibitors. However, at the present time, given that all the drugs are likely working by the same mechanism and the similarities in the blood pressure lowering effect, it is most likely that the near maximal blood pressure lowering of the different ACE inhibitors is the same.

### 2.3.2 What is the dose-ranging blood pressure lowering effect of ACE inhibitors as a class?

Based on the assumption of no difference between the different ACE inhibitors and the fact that the trough blood pressure lowering effects of the different ACE inhibitors were so similar, the data for 13 of the 14 drugs that had the manufacturers' dosage information available were pooled. Data were pooled for 13 ACE inhibitors by categorizing individual doses as proportions of the manufacturers' maximum recommended daily dose (Max). It is recognized that this approach has its limitations but it provided a non-arbitrary method for pooling the drugs. Using this method, as a class ACE inhibitors demonstrated a dose-response relationship. A dose of 1/16 Max had no measurable blood pressure lowering effect. A dose of 1/8 or 1/4 Max achieved a blood pressure lowering effect that was 60 to 70% of the blood pressure lowering effect of the maximum recommended dose. A dose of 1/2 Max achieved a blood pressure lowering effect that was 90% of the maximum recommended dose.

Combining the effects of half maximum recommended doses and above gives a reasonable estimate of the near maximal trough blood pressure lowering efficacy for the ACE inhibitors as a class, -8 mm Hg for SBP and -5 mm Hg for DBP. This was accompanied by an average reduction in pulse pressure of 3 mm Hg. This is quite a

modest effect and is likely considerably less than most clinicians would estimate can be achieved with these drugs. However, this effect is at trough and is obtained after subtracting the placebo effect which, on average, reduced blood pressure by 3/4 mm Hg. Furthermore, most doctors probably do not measure blood pressure in their patients at trough. In this review, there were much less data for blood pressure measured 1 to 12 hours after the doses. From these data, we were able to estimate the average effect of ACE inhibitors 1 to 12 hours after the dose and it was modestly higher, averaging -11.4/-6.4 mm Hg.

### 2.3.3 For each ACE inhibitor, do the manufacturer's dosage recommendations coincide with the findings of this review?

Assuming that the lowest effective dose should be the manufacturer's recommended starting dose, for 6 of the ACE inhibitors there is agreement between the manufacturer's recommended dose and the lowest effective dose determined by this systematic review (see Table 2.21).

**Table 2.21: Comparison of manufacturers' dosage recommendations and findings of this review**

| ACE Inhibitor | Lowest effective dose (mg/day) | Manufacturer's recommended starting dose (mg/day) | Lowest dose with near maximal BP lowering (mg/day) | Manufacturer's recommended maximum dose (mg/day) |
|---|---|---|---|---|
| benazepril | 20 | 10 | 20 | 40 |
| captopril | 37.5 | 50 | 37.5 | 150 |
| cilazapril | 2.5 | 2.5 | 2.5 | 10 |
| enalapril | 5 | 5 | 20 | 40 |
| fosinopril | 10-20 | 10 | 20 | 40 |
| imidapril | Not estimable | 5 | Not estimable | 20 |
| lisinopril | 10 | 10 | 10 | 80 |
| moexipril | 15 | 7.5 | Not estimable | 30 |
| perindopril | 4 | 4 | 4 | 8 |
| quinapril | Not estimable | 10 | Not estimable | 40 |
| ramipril | 5 | 2.5 | 5 | 20 |
| temocapril | Not estimable | 1 | Not estimable | 4 |
| trandolapril | 1 | 1 | 1 | 4 |

For benazepril, moexipril and ramipril, the lowest effective doses were determined to be higher than the manufacturer's recommended starting doses. Three of the ACE inhibitors (imidapril, quinapril and temocapril) did not have data available at lower doses to determine the lowest effective dose and thus no comparison could be made with the manufacturer's recommendations. For one ACE inhibitor, captopril, the lowest effective dose from this review was less than that which the manufacturer recommended. Spirapril is not shown in Table 2.21 as it has no manufacturer's recommended dose that we are aware of.

For 9 of the ACE inhibitors the lowest dose with near maximal blood pressure lowering was achieved at 1/4 to 1/2 of the manufacturer's recommended maximum daily dose. For lisinopril, most of the blood pressure lowering effect was achieved at only 1/8 of the recommended maximum dose. Quinapril and three other ACE inhibitors (imidapril, moexipril and temocapril) did not have data at higher doses to determine the lowest dose with near maximal blood pressure lowering.

### 2.3.4 What is the effect of ACE inhibitors on blood pressure variability?

The endpoint variabilities of the ACE inhibitor and placebo groups were compared in order to determine the effect of ACE inhibitors on blood pressure variability. Compared with placebo, ACE inhibitors did not change the variability in blood pressure. It appears that blood pressure criteria for entry into the trial do have an effect on the variability at baseline. In the trials with DBP entry criteria, the baseline standard deviations were substantively lower than the endpoint values in the ACE inhibitor and placebo groups. This effect is likely due to truncation of the distribution of blood pressures at the threshold and due to participants with slightly lower DBP than the threshold level for entry into the trial being entered as having a DBP at the threshold.

### 2.3.5 Is there evidence of a dose-response relationship for heart rate?

There is a possibility of selective reporting bias of resting heart rate since less than 20% of the trials reported data for this outcome. Based on the few trials for which data were available, there were insufficient data at higher doses to determine a dose-related effect on heart rate. The available data demonstrate that for all doses ACE inhibitors did not have an effect on resting heart rate.

### 2.3.6 Is there evidence of a dose-response relationship for withdrawals due to adverse effects?

There were not enough data to construct a meaningful dose-response relationship for individual ACE inhibitors and when combined there still were insufficient data at higher doses to determine a dose-related effect on WDAE. The available data demonstrate that for all doses ACE inhibitors did not change WDAE compared with placebo. However, only about half the trials reported the number of WDAE, so selective reporting bias is a distinct possibility. A description of the type and severity of the adverse effects that led to premature withdrawal was rarely reported. Short-term trials are not the best type of trial to assess adverse effects and longer trials and other types of data can assist, such as non-randomized trials or post-marketing surveillance studies. However, there is no justification for not reporting all withdrawals due to adverse effects in all completed trials.

### 2.3.7 Limitations of the review

Many trials required imputation of the standard deviations of the blood pressure change because they did not report these values. However, our average estimates of the blood pressure lowering effect of these drugs were insensitive to the imputation strategy used.

One of the main limitations of this review is that not all the trials assessing the efficacy of ACE inhibitors have been published. We know that because many of the doses that have been approved by regulators are not included in this review. For example, quinapril has been approved for a dose range of 10 to 40 mg in Canada and 10 to 80 mg in the USA. We only found data for the effect of 20 mg of quinapril and we know that trials must have been completed and provided to the regulators for the other doses.

The use of maximum recommended dose by the manufacturer as a way of trying to compare equivalent doses of the drugs is imperfect but served our purposes in this review. Since this is planned to be published as a Cochrane review, it will be necessary to update it at least every 2 years. As more data for a wider range of doses become available, it may be possible to estimate the ED-50 for each drug and thus use that criterion to combine the equieffective doses of the different ACE inhibitors.

### 2.3.8 What are the potential sources of bias?

#### 2.3.8.1 Sequence generation, allocation concealment

Nearly all the trial publications simply reported that the trial was "randomized" but did not provide any details about the randomization method or the method of allocation concealment. Details of the methods for generation of the sequence of allocations or allocation concealment were reported in only 5 of the 92 (5.4%) included studies. Such vague reporting is insufficient to be confident that the allocation sequence was properly randomized and adequately concealed given the fact that many investigators use the term "randomized" when it is not justified. Authors should report their methods of sequence generation and allocation concealment clearly.

#### 2.3.8.2 Blinding bias

Nearly all the trial publications simply reported that the trial was "double-blind" but did not provide any details about the blinding methods. There was a potential for loss of blinding in the trials studying ACE inhibitors since these drugs have a well-known side effect that is unique to this class of drugs, namely a refractory cough. However, none of the included studies reported a significantly higher rate of cough or withdrawals due to cough over placebo in patients treated with ACE inhibitors. The success of blinding in patients or investigators was not assessed in any of the included trials.

#### 2.3.8.3 Attrition bias

It is unlikely that attrition bias would have had an impact on the systematic review since 89 to 100 percent of patients randomized to fixed-dose monotherapy in each trial completed the double-blind treatment period.

#### 2.3.8.4 Selective reporting bias

This would not affect the blood pressure measurements as these were the primary outcome of most of these trials. As mentioned above, there is a potential for selective reporting bias for heart rate and withdrawals due to adverse effects.

#### 2.3.8.5 Other potential sources of bias

Another potential source of bias that we became aware of in working on this review is selection bias. One of the exclusion criteria reported in nearly all trials was participants with a known hypersensitivity to ACE inhibitors. Although hypersensitivity to an ACE inhibitor may not have any connection to cough, it suggests that investigators have knowledge of each participant's prior experience with this drug class and thus may select for patients who have responded favorably to ACE inhibitors in terms of blood pressure lowering or have been found to tolerate ACE inhibitor treatment. However, it was not possible to prove selection bias as none of the included trials described in detail these details of patient recruitment.

One could hypothesize that those patients who are known responders in previous trials tend to be recruited to participate in subsequent trials, so more recent trials may show a greater magnitude of blood pressure lowering efficacy. This hypothesis was tested by performing a post-hoc tertile analysis according to the year of trial publication. The trials were divided into three groups and the oldest group of trials was compared with the group of most recent trials for mean blood pressure lowering efficacy. This analysis did not show a statistically significant difference in blood pressure lowering between the oldest and most recent group of trials. This finding does not support the hypothesis; however, it does not rule out the possibility of some selection bias occurring during both the older and newer trials.

#### 2.3.8.6 Publication bias

Yet another source of bias that may skew the results of systematic reviews is publication bias, which results from the selective publication of trials with positive results. This review was evaluated for the existence of publication bias since it only included and appraised published trial evidence. In the absence of bias, the funnel plot should resemble a symmetrical inverted funnel since the precision in the estimation of the true blood pressure lowering decreases as the study size decreases. Thus small studies will scatter more widely at the bottom of the graph [166]. The most common way to investigate whether or not a review is subject to publication bias is to examine for funnel plot asymmetry as smaller studies with null results remained unpublished. The funnel

plots generated from the results of the ACE inhibitor review did not demonstrate any signs of asymmetry.

A post-hoc tertile analysis was conducted for the class of ACE inhibitors to corroborate the reasonable symmetry observed in the funnel plots. The studies were divided into three groups according to sample size in order to compare the mean effect estimates between the largest trials (highest tertile) and smallest trials (lowest tertile). The results of this analysis demonstrated no statistically significantly difference in the estimate of the blood pressure lowering efficacy of ACE inhibitors between the smallest and largest trials. In this case, publication bias did not impact our estimate of the true effect size.

Visual examination of the funnel plots also showed little resemblance to a characteristic inverted funnel as there was an absence of smaller sized studies that scattered more widely at the bottom of the graph. One explanation for this is that smaller studies included in this systematic review were conducted and analyzed with similar methodological rigor as larger trials so the reported treatment effects are of similar precision. Another possibility is that smaller studies are of lower methodological quality than larger studies and have less precise estimates of the effect size, but those trials with little or no reduction in blood pressure and those trials with exaggerated effect estimates remain unpublished.

The results of this review underscore the need for all studies, regardless of the findings, to be published and accessible for secondary analysis. Trial registration has been recognized in order to improve transparency in research and knowledge sharing. In recent years, regulatory bodies around the world, led by the World Health Organization (WHO), have set standards for trial registration and reporting and are urging research institutions and companies to register all medical studies that test treatments on humans [167]. Initiatives such as the WHO's International Clinical Trials Registry Platform will help improve transparency and reduce the risk of publication bias skewing the results of future systematic reviews.

## 2.4 Reviewers' conclusions

### 2.4.1 Implications for practice

#### 2.4.1.1 Specific findings of the review

1. The review provides data on the dose-related blood pressure lowering efficacy of 14 different ACE inhibitors at trough. The best estimate of the blood pressure lowering efficacy of these 14 drugs ranges from -6/-4 to -9/-5 mm Hg. The data do not suggest that any one ACE inhibitor is better or worse at lowering blood pressure when used at doses of one-half the manufacturer's maximal recommended dose and above.
2. A dose-response relationship for the blood pressure lowering effect of the ACE inhibitors was evident. A dose of 1/16 of the maximum recommended dose had no measurable blood pressure lowering effect. A dose of 1/8 or 1/4 of the maximum recommended daily achieved a blood pressure lowering effect that was 60 to 70% of the blood pressure lowering effect of the maximum recommended dose. A dose of 1/2 of the maximum recommended dose achieved a blood pressure lowering effect that was 90% of the maximum recommended dose.
3. ACE inhibitor doses above the maximum recommended dose did not significantly lower blood pressure more than the maximum recommended dose.
4. Combining the effects of half maximum recommended doses and higher gives an estimate of the average trough blood pressure lowering efficacy for ACE inhibitors as a class of drugs of -8 mm Hg for SBP and -5 mm Hg for DBP.
5. ACE inhibitors reduced blood pressure measured 1 to 12 hours after the dose by about 11/6 mm Hg.
6. ACE inhibitors reduced trough pulse pressure by about 3 mm Hg.
7. ACE inhibitors did not significantly affect resting blood pressure variability or heart rate.
8. All doses of ACE inhibitors, whether analyzed individually or combined, did not change WDAE as compared to placebo; however, this outcome was not reported for about half the trials so there is judged to be a high risk of selective reporting bias.

#### 2.4.1.2 Implications of these findings

This systematic review provides the best available published evidence about the dose-related blood pressure lowering efficacy of ACE inhibitors for the treatment of primary hypertension. These findings have the potential to change prescribing behavior and drug funding policies around the world. The evidence from this review suggests that there are no clinically meaningful differences between ACE inhibitors for lowering blood pressure. Thus, substantial cost savings can be achieved by prescribing the least expensive ACE inhibitor.

The major limitation of this review is that it is limited to published trials and it is evident that a lot of trials that manufacturers would have needed to gain marketing approval have not been published. Thus even though there was no evidence of publication bias using standard methods to asses this, there remains a high risk for publication bias. It is also estimated that there is a high risk of patient selection bias that could have led to overestimation of the blood pressure lowering effect. For these reasons the magnitude of blood pressure lowering found is this review is probably an overestimate of the true effect. This observation makes even more surprising that the estimates of trough and peak blood pressure lowering effects of the ACE inhibitors are modest at best and lower than commonly believed can be achieved by this class of drugs. In addition, the review demonstrates that 60 to 70% of the blood pressure lowering effect occurs with recommended starting doses and that there is no evidence for using doses higher than half the manufacturer's maximum recommended daily dose. If physicians prescribing ACE inhibitors were aware of this evidence they would prescribe lower doses leading to substantial cost savings, and possibly leading to a reduction in dose-related adverse events.

This review did not provide any evidence of an increase in withdrawals due to adverse effects overall and the trend towards higher withdrawals with higher doses was not statistically significant. However, this finding is severely limited by the short duration of the included trials and a high risk of both selective reporting bias and patient selection bias. Therefore, this systematic review is not a good measure of the incidence of adverse effects of this class of drugs.

### 2.4.2 Implications for research

1. It is evident that for some of the ACE inhibitors studied (eg. quinapril and others) trials reporting data on doses recommended for use are not published. It should be mandatory that all clinical trials be registered and the results of these trials be published or otherwise made available in full detail.
2. Full dose-response data for doses within the recommended and beyond the recommended dose range are needed to properly analyze the dose-response relationship for each ACE inhibitor.
3. Trials should measure and report blood pressure data for peak effects as well as trough effects.
4. All trials should report withdrawals due to adverse effects and serious adverse events.

## 2.5 References


1. Heran BS, Wong MMY, Wright JM. Dose-related blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors in the treatment of primary hypertension. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003823. DOI: 10.1002/14651858.CD003823.

2. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

3. Musini VM. A Systematic Review of the blood pressure lowering efficacy of thiazide and loop diuretics in the treatment of primary hypertension. M.Sc. Thesis, University of British Columbia 2000.

4. Heran BS, Jauca CD, Wright JM. Development of an optimal search strategy for finding trials demonstrating ACE inhibitor blood pressure lowering efficacy. 10th International Cochrane Colloquium, Stavanger, Norway 2002.

5. Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 6. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

6. Jadad AR, Moore RA, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trials 1996; 17:1-12.

7. Bucher HC, Guyatt GH, Griffith LE, Walker SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology 1997; 50(6):683-691.

8. Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003; 326:472-476.

9. Bainbridge AD, MacFadyen RJ, Stark S, Lees KR, Reid JL. The antihypertensive efficacy and tolerability of a low dose combination of ramipril and felodipine ER in mild to moderate essential hypertension. British Journal of Clinical Pharmacology 1993; 36(4):323-30.

10. Bakris G, Sica D, Ram V, Fagan T, Vaitkus PT, Anders RJ, et al. A comparative trial of controlled-onset, extended-release verapamil, enalapril, and losartan on blood pressure and heart rate changes. American Journal of Hypertension 2002; 15(1 Pt 1):53-7.

11. Beaulieu M, Nadeau A, Lacourciere Y, Cleroux J. Post-exercise reduction in blood pressure in hypertensive subjects: Effects of angiotensin converting enzyme inhibition. British Journal of Clinical Pharmacology 1993; 36(4):331-8.

12. Beaulieu M, Lacourciere Y, Cleroux J. Unchanged neurogenic vasoconstrictor response after exercise during angiotensin converting enzyme inhibition with fosinopril. American Journal of Hypertension 1994; 7(8):763-6.

13. Bergstrand R, Herlitz H, Johannson S, Berglund G, Vedin A, Wilhelmsson C, et al. Effective dose range of enalapril in mild to moderate essential hypertension. British Journal of Clinical Pharmacology 1985; 19(5):605-11.

14. Bohlen L, Bienz R, Doser M, Papiri M, Shaw S, Riesen W, et al. Metabolic neutrality of perindopril: Focus on insulin sensitivity in overweight patients with essential hypertension. Journal of Cardiovascular Pharmacology 1996; 27(6):770-6.

15. Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. Journal of Human Hypertension 1994; 8(3):155-62.

16. Canter DA, Texter MJ, McLain RW. Ambulatory blood pressure monitoring can play an integral role in patient selection, dosage adjustment and efficacy assessment in clinical trials of antihypertensive agents. Journal of Hypertension - Supplement 1994; 12(7):S33-S38.

17. Cleroux J, Beaulieu M, Kouame N, Lacourciere Y. Comparative effects of quinapril, atenolol, and verapamil on blood pressure and forearm hemodynamics during handgrip exercise. American Journal of Hypertension 1994; 7(6):566-70.

18. Cuspidi C, Lonati L, Sampieri L, Leonetti G, Muiesan ML, Agabiti-Rosei E, et al. Lack of effect of short-term lisinopril administration on left ventricular filling dynamics in hypertensive patients with diastolic dysfunction. Blood Pressure 1997; 6(5):307-12.

19. Duprez D, Clement DL. Vasodilator effects of enalapril in patients with arterial hypertension. Acta Cardiologica 1986; 41(5):359-64.

20. Fagard R, Lijnen P, Pardaens K, Thijs L, Vinck W. A randomised, placebo-controlled, double-blind, crossover study of losartan and enalapril in patients with essential hypertension. Journal of Human Hypertension 2001; 15(3):161-7.

21. Gall MA, Rossing P, Skott P, Hommel E, Mathiesen ER, Gerdes LU, et al. Placebo-controlled comparison of captopril, metoprolol, and hydrochlorothiazide therapy in non-insulin-dependent diabetic patients with primary hypertension. American Journal of Hypertension 1992; 5(5 Pt 1):257-65.

22. Gans RO, Stehouwer CD, Bilo HJ, Goggin T, Kraaij CJ, Donker AJ, et al. Effect of cilazapril on glucose tolerance and lipid profile in hypertensive patients with non-

insulin-dependent diabetes mellitus. Netherlands Journal of Medicine 1993; 43(3-4):163-73.

23. Gleerup G, Petersen JR, Mehlsen PJ, Winther K. Effect of spirapril and hydrochlorothiazide on platelet function and euglobulin clot lysis time in patients with mild hypertension. Angiology 1996; 47(10):951-6.

24. Guitard C, Alvisi V, Maibach E, Franck J, Cocco G, Boxho G, et al. Placebo-controlled comparison of spirapril at 6, 12 and 24 mg/day in mild to severe essential hypertension. Blood Pressure 1994; Supplement. 2:81-7.

25. Gupta RK, Kjeldsen SE, Krause L, Kneisley J, Posvar E, Weder AB, et al. Hemodynamic effects of quinapril, a novel angiotensin-converting enzyme inhibitor. Clinical Pharmacology & Therapeutics 1990; 48(1):41-9.

26. Gupta RK, Kjeldsen SE, Motley E, Weder AB, Zweifler AJ, Julius S. Platelet function during antihypertensive treatment with quinapril, a novel angiotensin converting enzyme inhibitor. Journal of Cardiovascular Pharmacology 1991; 17(1):13-9.

27. Homuth V, Faulhaber HD, Loose U, Loffler K, Luft FC. Usefulness of piretanide plus ramipril for systemic hypertension: a multicenter trial. American Journal of Cardiology 1993; 72(9):666-71.

28. Hu Y, Zhu J. Quality of life of patients with mild hypertension treated with captopril: A randomized double-blind placebo-controlled clinical trial. Chinese Medical Journal 1999; 112(4):302-7.

29. Kahan T, Eliasson K. The influence of long-term ACE inhibitor treatment on circulatory responses to stress in human hypertension. American Journal of Hypertension 1999; 12(12 Pt 1-2):1188-94.

30. Karlberg BE, Lindstrohm T, Rosenqvist U, Ohman KP. Efficacy, tolerance and hormonal effects of a new oral angiotensin converting enzyme inhibitor, ramipril (HOE 498), in mild to moderate primary hypertension. American Journal of Cardiology 1987; 59(10):104D-9D.

31. Kjeldsen SE, Gupta RK, Krause L, Weder AB, Julius S. Does blood pressure reduction necessarily compromise cardiac function or renal hemodynamics? Effects of the angiotensin-converting enzyme inhibitor quinapril. American Heart Journal 1992; 123(5):1433-8.

32. Lacourciere Y. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. International Journal of Clinical Practice 1999; 53(2):99-103.

33. Lavezzaro G, Ladetto PE, Valente M, Stramignoni D, Zanna C, Assogna G, et al. Ketanserin and captopril interaction in the treatment of essential hypertensives. Cardiovascular Drugs & Therapy 1990; 4 Suppl 1:119-22.

34. Leonetti G, Mazzola C, Pasotti C, Angioni L, Vaccarella A, Capra A, et al. Treatment of hypertension in the elderly: effects on blood pressure, heart rate, and physical fitness. American Journal of Medicine 1991; 90(3A):12S-3S.

35. Littler WA, West JW. Twenty-four hour action of ACE inhibitors. Journal of Human Hypertension 1990; 4 Suppl 4:13-6.

36. Louis WJ, Workman BS, Conway EL, Worland P, Rowley K, Drummer O, et al. Single-dose and steady-state pharmacokinetics and pharmacodynamics of perindopril in hypertensive subjects. Journal of Cardiovascular Pharmacology 1992; 20(3):505-11.

37. Miyajima E, Shigemasa T, Yamada Y, Tochikubo O, Ishii M. Angiotensin II blunts, while an angiotensin-converting enzyme inhibitor augments, reflex sympathetic inhibition in humans. Clinical and Experimental Pharmacology and Physiology 1999; 26(10):797-802.

38. Morgan TO, Anderson A, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. American Journal of Hypertension 2001; 14:241-7.

39. Petersen JR, Drabaek H, Gleerup G, Mehlsen J, Petersen LJ, Winther K. ACE inhibition with spirapril improves diastolic function at rest independent of vasodilation during treatment with spirapril in mild to moderate hypertension. Angiology 1996; 47(3):233-40.

40. Petrie JR, Morris AD, Ueda S, Small M, Donnelly R, Connell JM, et al. Trandolapril does not improve insulin sensitivity in patients with hypertension and type 2 diabetes: a double-blind, placebo-controlled crossover trial. Journal of Clinical Endocrinology & Metabolism 2000; 85(5):1882-9.

41. Petrov VV, Fagard RH, Lijnen PJ. T-lymphocyte and plasma angiotensin-converting enzyme activity during enalapril and losartan administration in humans. Journal of Cardiovascular Pharmacology 2001; 38(4):578-83.

42. Plouin PF, Battaglia C, Alhenc-Gelas F, Corvol P. Are angiotensin converting enzyme inhibition and aldosterone antagonism equivalent in hypertensive patients over fifty? American Journal of Hypertension 1991; 4(4 Pt 1):356-62.

43. Pritchard G, Lyons D, Webster J, Petrie JC, MacDonald TM. Indomethacin does not attenuate the hypotensive effect of trandolapril. Journal of Human Hypertension 1996; 10(11):763-7.

44. Pritchard G, Lyons D, Webster J, Petrie JC, MacDonald TM. Do trandolapril and indomethacin influence renal function and renal functional reserve in hypertensive patients? British Journal of Clinical Pharmacology 1997; 44(2):145-9.

45. Reisin E, Weir MR, Falkner B, Hutchinson HG, Anzalone DA, Tuck ML. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trial. Hypertension 1997; 30(1 Pt 1):140-5.

46. Salvetti A, Innocenti PF, Iardella M, Pambianco F, Saba GC, Rossetti M, et al. Captopril and nifedipine interactions in the treatment of essential hypertensives: a crossover study. Journal of Hypertension - Supplement 1987; 5(4):S139-S142.

47. Salvetti A, Circo A, Raciti S, Gulizia M, Cardillo R, Miceli S, et al. Captopril at 50 mg as well as at 100 mg once a day reduces blood pressure for up to 24 h: a double-blind randomized crossover study in mild to moderate hypertensives. Journal of Hypertension - Supplement 1988; 6(4):S666-S668.

48. Salvetti A, Arzilli F. Chronic dose-response curve of enalapril in essential hypertensives. An Italian multicenter study. American Journal of Hypertension 1989; 2(5 Pt 1):352-4.

49. Samuelsson O, Hedner T, Ljungman S, Herlitz H, Widgren B, Pennert K. A comparative study of lisinopril and atenolol on low degree urinary albumin excretion, renal function and haemodynamics in uncomplicated, primary hypertension. European Journal of Clinical Pharmacology 1992; 43(5):469-75.

50. Sassano P, Chatellier G, Amiot AM, Alhenc-Gelas F, Corvol P, Menard J. A double-blind randomized evaluation of converting enzyme inhibition as the first-step treatment of mild to moderate hypertension. Journal of Hypertension - Supplement 1984; 2(2):S75-S80.

51. Scholze J. Short report: Ramipril and hydrochlorothiazide combination therapy in hypertension: A clinical trial of factorial design. Journal of Hypertension 1993; 11(2):217-21.

52. Thurig C, Bohlen L, Schneider M, de Courten M, Shaw SG, Riesen W, et al. Lisinopril is neutral to insulin sensitivity and serum lipoproteins in essential hypertensive patients. European Journal of Clinical Pharmacology 1995; 49(1-2):21-6.

53. Tomei R, Rossi L, Carbonieri E, Franceschini L, Molon G, Zardini P. Antihypertensive effect of lisinopril assessed by 24-hour ambulatory monitoring: a double-blind, placebo-controlled, cross-over study. Journal of Cardiovascular Pharmacology 1992; 19(6):911-4.

54. Wiggam MI, Hunter SJ, Atkinson AB, Ennis CN, Henry JS, Browne JN, et al. Captopril does not improve insulin action in essential hypertension: a double-blind placebo-controlled study. Journal of Hypertension 1998; 16(11):1651-7.

55. Wilkins LH, Dustan HP, Walker JF, Oparil S. Enalapril in low-renin essential hypertension. Clinical Pharmacology & Therapeutics 1983; 34(3):297-302.

56. Wing LM, Chalmers JP, West MJ, Bune AJ, Russell AE, Elliott JM, et al. Treatment of hypertension with enalapril and hydrochlorothiazide or enalapril and atenolol: contrasts in hypotensive interactions. Journal of Hypertension - Supplement 1987; 5(5):S603-S606.

57. Wing LM, Chalmers JP, West MJ, Russell AE, Morris MJ, Cain MD, et al. Enalapril and atenolol in essential hypertension: attenuation of hypotensive effects in combination. Clinical and Experimental Hypertension. Part A, Theory and Practice 1988;10(1):119-33.

58. Youssef S, Osman L, Sabbour MS. Serum lipoprotein profile under different antihypertensive therapy. Cardiovascular Risk Factors 1993; 3(2):107-11.

59. Zanchetti A, Omboni S. Comparison of candesartan versus enalapril in essential hypertension. American Journal of Hypertension 2001; 14(2):129-34.

60. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. Archives of Family Medicine 1996; 5(1):17-24.

61. Gomez HJ. Dose-response studies with benazepril in mild to moderate hypertension. Clinical Cardiology 1991; 14(8 Suppl 4):IV22-IV27.

62. Kuschnir E, Acuna E, Sevilla D, Vasquez J, Bendersky M, Resk J, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. Clinical Therapeutics 1996; 18(6):1213-24.

63. McFate SW, Gomez HJ. The use of benazepril in hypertensive patients age 55 and over. Clinical Cardiology 1991; 14(8 SUPPL. 4):79-82.

64. Moser M, Abraham PA, Bennett WM, Brachfeld N, Goodman RP, McKenney JM, et al. The effects of benazepril, a new angiotensin-converting enzyme inhibitor, in mild to moderate essential hypertension: a multicenter study. Clinical Pharmacology & Therapeutics 1991; 49(3):322-9.

65. Pool J, Kaihlanen P, Lewis G, Ginsberg D, Oparil S, Glazer R, et al. Once-daily treatment of patients with hypertension: a placebo-controlled study of amlodipine and benazepril vs amlodipine or benazepril alone. Journal of Human Hypertension 2001; 15(7):495-8.

66. Weinberger MH, Black HR, Lasseter KC, Lewis GP, MacLeod CM, Pascual AV, et al. Diurnal blood pressure in patients with mild-to-moderate hypertension treated

with once-daily benazepril hydrochloride. Clinical Pharmacology & Therapeutics 1990; 47(5):608-17.

67. Whalen J, Skalky C, DeSilva J, Weber M. Peak and trough effects of 3 once daily dose levels of benazepril in mild-moderate hypertension. American Journal of Hypertension 1989; 2(5 Pt 2):45A.

68. Drayer JI, Weber MA. Monotherapy of essential hypertension with a converting-enzyme inhibitor. Hypertension 1983; 5(5 Pt 2):III108-III113.

69. Dupui P, Larrue V, Pavy-Le Traon A, Allavoine T, Geraud G, Bes A. Effects of a captopril-induced decrease of the arterial blood pressure on the cerebral blood flow of elderly subjects with moderate hypertension. Circulation et Metabolisme du Cerveau 1993; 10(3-4):143-56.

70. Larrue V, Dupui P, Pavy-Le Traon A, Allavoine T, Geraud G, Bes A. Cerebral blood flow changes induced by a chronic treatment with captopril in previously untreated elderly hypertensive subjects. Archives des Maladies du Coeur et des Vaisseaux 1994; 87(8):997-1000.

71. Kayanakis JG, Baulac L. Comparative study of once-daily administration of captopril 50 mg, hydrochlorothiazide 25 mg and their combination in mild to moderate hypertension. British Journal of Clinical Pharmacology 1987; 23 Suppl 1:89S-92S.

72. Muiesan G, Agabiti-Rosei E, Buoninconti R, Cagli V, Carotti A, Corea L, et al. Antihypertensive efficacy and tolerability of captopril in the elderly: comparison with hydrochlorothiazide and placebo in a multicentre, double-blind study. Journal of Hypertension - Supplement 1987; 5(5):S599-S602.

73. Schoenberger JA, Wilson DJ. Once-daily treatment of essential hypertension with captopril. Journal of Clinical Hypertension 1986; 2(4):379-87.

74. Veterans Administration Cooperation Study Group on Antihypertensive Agents. Low-dose captopril for the treatment of mild to moderate hypertension. I. Results of a 14-week trial. Archives of Internal Medicine 1984; 144(10):1947-53.

75. Veterans Administration Cooperation Study Group on Antihypertensive Agents. Racial differences in response to low-dose captopril are abolished by the addition of hydrochlorothiazide. British Journal of Clinical Pharmacology 1982; 14 Suppl 2:97S-101S.

76. Boeijinga JK, Kraaij CJ, Kleinbloesem CH, Cohen AF, Breimer DD. The influence of cilazapril on anticoagulation in hypertensive patients treated with coumarins. Current Therapeutic Research, Clinical & Experimental 1993; 54(4):443-51.

77. Carlsen JE, Buchmann M, Hoglund C, Pellinen T, Honkanen T, Soerensen OH, et al. 24-hour antihypertensive effect of oral cilazapril? A placebo-controlled study

evaluating 1, 2.5 and 5 mg once daily. Clinical Drug Investigation 1995; 10(4):221-7.

78. Fernandez PG, Bolli P, Lee C. The 24 h blood pressure responses of hypertensives to a once-a-day cilazapril regimen. Canadian Journal of Cardiology 1990; 6(2):53-8.

79. Fernandez PG, Bolli P, Lee C, Vasdev S. Cilazapril inhibits vascular responses to baroreflex-stimulated sympathetic neural activity in hypertensive patients. Canadian Journal of Cardiology 1990; 6(1):9-14.

80. Guntzel P, Kobrin I, Pasquier C, Zimlichman R, Viskoper JR. The effect of cilazapril, a new angiotensin converting enzyme inhibitor, on peak and trough blood pressure measurements in hypertensive patients. Journal of Cardiovascular Pharmacology 1991; 17(1):8-12.

81. Kobrin I, Guntzel P, Viskoper R, Paran E, Zimlichman R. Antihypertensive duration of action of cilazapril in patients with mild to moderate essential hypertension. Drugs 1991; 41 Suppl 1:31-6.

82. Krum H, Jackson B, Conway EL, Howes LG, Johnston CI, Louis WJ. Steady-state pharmacokinetics and pharmacodynamics of cilazapril in the presence and absence of cyclopenthiazide. J Cardiovasc Pharmacol 1992; 20(3):451-7.

83. Lacourciere Y, Leenen F, Rangno R, Spence JD, Lenis JH, Myers MG. Discrepancies between clinic and ambulatory blood pressure responses to cilazapril therapy. Canadian Journal of Cardiology 1994; 10(6):605-10.

84. Mroczek WJ, Klein J, Burris JF. Dose-finding study of cilazapril (Inhibace) in patients with uncomplicated essential hypertension. Clinical and Experimental Hypertension. Part A, Theory and Practice 1991; 13(8):1415-32.

85. Poirier L, Pyzyk M, Provencher P, Lacourciere Y. Comparative effects of 2.5 and 5 mg cilazapril versus placebo on daily blood pressure load. American Journal of Hypertension 1991; 4(11):913-5.

86. Lacourciere Y, Poirier L, Pyzyk M. [2.5 and 5 mg cilazapril once daily in comparison with placebo in hypertension. A comparative study with ambulatory 24-hour monitoring]. [German]. Cardiology 1993; 82 Suppl 2:78-82.

87. Pordy RC. Cilazapril plus hydrochlorothiazide: improved efficacy without reduced safety in mild to moderate hypertension. A double-blind placebo-controlled multicenter study of factorial design. Cardiology 1994; 85(5):311-22.

88. Prager G, Klein P, Schmitt M, Prager R. Antihypertensive efficacy of cilazapril 2.5 and 5.0 mg once-daily versus placebo on office blood pressure and 24-hour blood pressure profile. Journal of Cardiovascular Pharmacology 1994; 24 Suppl 3:S93-S99.

89. Uusitupa M, Korhonen M, Litmanen H, Niskanen L, Vaisanen S, Rauramaa R. Effects of moderate salt restriction alone and in combination with cilazapril on office and ambulatory blood pressure. Journal of Human Hypertension 1996; 10(5):319-26.

90. White WB, McCabe EJ, Hager WD, Schulman P. The effects of the long-acting angiotensin-converting enzyme inhibitor cilazapril on casual, exercise, and ambulatory blood pressure. Clinical Pharmacology & Therapeutics 1988; 44(2):173-8.

91. Yodfat Y, Zimilchman R. Dose-finding and dose justification of once-daily cilazapril in combination with hydrochlorothiazide in non-obese patients with mild-to-moderate essential hypertension. Journal of Drug Development 1993; 6(3):117-21.

92. Applegate WB, Cohen JD, Wolfson P, Davis A, Green S. Evaluation of blood pressure response to the combination of enalapril (single dose) and diltiazem ER (four different doses) in systemic hypertension. American Journal of Cardiology 1996; 78(1):51-5.

93. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. American Journal of Hypertension 1998; 11(1 Pt 1):23-30.

94. Gerritsen TA, Bak AA, Stolk RP, Jonker JJ, Grobbee DE. Effects of nitrendipine and enalapril on left ventricular mass in patients with non-insulin-dependent diabetes mellitus and hypertension. Journal of Hypertension 1998; 16(5):689-96.

95. Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snavely DB, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension 1995; 25(6):1345-50.

96. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC. Combined enalapril and felodipine extended release (ER) for systemic hypertension. American Journal of Cardiology 1997; 79(4):431-5.

97. Guitard C, Lohmann FW, Alfiero R, Ruina M, Alvisi V. Comparison of efficacy of spirapril and enalapril in control of mild-to-moderate hypertension. Cardiovascular Drugs and Therapy 1997; 11(3):449-57.

98. Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, Oddou-Stock P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. Journal of Hypertension 1996; 14(9):1147-51.

99. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. New England Journal of Medicine 1998; 338(12):784-90.

100. Kuppers HE, Jager BA, Luszick JH, Grave MA, Hughes PR, Kaan EC. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild-to-moderate essential hypertension. Journal of Hypertension 1997; 15(1):93-7.

101. Levine JH, Ferdinand KC, Cargo P, Laine H, Lefkowitz M. Additive effects of verapamil and enalapril in the treatment of mild to moderate hypertension. American Journal of Hypertension 1995; 8(5 Pt 1):494-9.

102. Oparil S. Eprosartan versus enalapril in hypertensive patients with angiotensin-converting enzyme inhibitor-induced cough. Current Therapeutic Research, Clinical & Experimental 1999; 60(1):1-4.

103. Prichard BNC. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild to moderate essential hypertension. Blood Pressure 2002; 11(3):2002.

104. Roca-Cusachs AT. Nitrendipine and enalapril combination therapy in mild to moderate hypertension: Assessment of dose-response relationship by a clinical trial of factorial design. Journal of Cardiovascular Pharmacology 2001; 38(6):2001.

105. Simon G, Morioka S, Snyder DK, Cohn JN. Increased renal plasma flow in long-term enalapril treatment of hypertension. Clinical Pharmacology & Therapeutics 1983; 34(4):459-65.

106. Morioka S, Simon G, Cohn JN. Cardiac and hormonal effects of enalapril in hypertension. Clinical Pharmacology & Therapeutics 1983 Nov;34(5):583-9.

107. Smith DHG, Neutel JM, Morgenstern P. Once-daily telmisartan compared with enalapril in the treatment of hypertension. Advances in Therapy 1998; 15(4):229-40.

108. Smith DH, Matzek KM, Kempthorne-Rawson J. Dose response and safety of telmisartan in patients with mild to moderate hypertension. Journal of Clinical Pharmacology 2000; 40(12 Pt 1):1380-90.

109. Waeber B, Detry JM, Dahlof B, Puig JG, Gundersen T, Hosie J, et al. Felodipine-metoprolol combination tablet: a valuable option to initiate antihypertensive therapy? American Journal of Hypertension 1999; 12(9 Pt 1):915-20.

110. Whelton A, Dunne B, Jr., Glazer N, Kostis JB, Miller WE, Rector DJ, et al. Twenty-four hour blood pressure effect of once-daily lisinopril, enalapril, and placebo in patients with mild to moderate hypertension. Journal of Human Hypertension 1992; 6(4):325-31.

111. White WB, Sica DA, Calhoun D, Mansoor GA, Anders RJ. Preventing increases in early-morning blood pressure, heart rate, and the rate-pressure product with controlled onset extended release verapamil at bedtime versus enalapril, losartan, and placebo on arising. American Heart Journal 2002; 144(4):657-65.

112. Fernandez M, Madero R, Gonzalez D, Camacho P, Villalpando J, Arriaga J. Combined versus single effect of fosinopril and hydrochlorothiazide in hypertensive patients. Hypertension 1994; 23(1 Suppl):I207-I210.

113. Ford NF, Fulmor IE, Nichola PS, Alpin PG, Herron JM. Fosinopril monotherapy: relationship between blood pressure reduction and time of administration. Clinical Cardiology 1993; 16(4):324-30.

114. Pizarro M, Lima MJ, Domingues J, Gouveia AC, Monteiro A, Carrageta M, et al. [Antihypertensive effect of fosinopril in mild hypertension]. [Portuguese]. Revista Portuguesa de Cardiologia 460; 15(6):495-7.

115. Pool JL. Antihypertensive effect of fosinopril, a new angiotensin converting enzyme inhibitor: Findings of the fosinopril study group II. Clinical Therapeutics 1990; 12(6):520-33.

116. Pool JL, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. American Journal of Hypertension 1997; 10(1):117-23.

117. Zamboulis C, Karagiannis A, Gotzamani-Psarrakou A, Deligianni K, Spyridonidis T, Fragos S, et al. Effects of fosinopril on renal function in patients with mild to moderate essential hypertension. Clinical Drug Investigation 1996; 12(5):251-8.

118. Vandenburg MJ, Mackay EM, Dews I, Pullan T, Brugier S. Dose finding studies with imidapril--a new ACE inhibitor. British Journal of Clinical Pharmacology 1994; 37(3):265-72.

119. Black HR, Graff A, Shute D, Stoltz R, Ruff D, Levine J, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. Journal of Human Hypertension 1997; 11(8):483-9.

120. Chan P, Lin CN, Tomlinson B, Lin TH, Lee YS. Additive effects of diltiazem and lisinopril in the treatment of elderly patients with mild-to-moderate hypertension. American Journal of Hypertension 1997; 10(7 Pt 1):743-9.

121. Chrysant SG, Angelo JE, Chinoy DA, Galichia JP, Glazer N, Harris SI, et al. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination: A large multicenter study. Archives of Internal Medicine 1994; 154(7):737-43.

122. Gomez HJ, Cirillo VJ, Sromovsky JA, Otterbein ES, Shaw WC, Rush JE, et al. Lisinopril dose-response relationship in essential hypertension. British Journal of Clinical Pharmacology 1989; 28(4):415-20.

123. Koch B, Oparil S, Stimpel M. Co-administration of an ACE-inhibitor (moexipril) and hormonal replacement therapy in postmenopausal women. Journal of Human Hypertension 1999; 13(5):337-42.

124. Mroczek WJ, Stimpel M. A double-blind evaluation of moexipril versus hydrochlorothiazide in hypertension. Advances in Therapy 1996; 13(2):79-87.

125. Persson B, Stimpel M. Evaluation of the antihypertensive efficacy and tolerability of moexipril, a new ACE inhibitor, compared to hydrochlorothiazide in elderly patients. European Journal of Clinical Pharmacology 1996; 50(4):259-64.

126. White WB, Whelton A, Fox AA, Stimpel M, Kaihlanen PM. Tricenter assessment of the efficacy of the ACE inhibitor, moexipril, by ambulatory blood pressure monitoring. Journal of Clinical Pharmacology 1995; 35(3):233-8.

127. Brown CL, Backhouse CI, Grippat JC, Santoni JP. The effect of perindopril and hydrochlorothiazide alone and in combination on blood pressure and on the renin-angiotensin system in hypertensive subjects. European Journal of Clinical Pharmacology 1990; 39(4):327-32.

128. Chrysant SG, McDonald RH, Wright JT, Barden PL, Weiss RJ. Perindopril as monotherapy in hypertension: a multicenter comparison of two dosing regimens. Clinical Pharmacology & Therapeutics 1993; 53(4):479-84.

129. Luccioni R, Frances Y, Gass R, Schwab C, Santoni JP, Perret L. Evaluation of the dose-effect relationship of a new ace inhibitor (perindopril) by an automatic blood pressure recorder. European Heart Journal 1988; 9(10):1131-6.

130. Myers MG. A dose-response study of perindopril in hypertension: Effects on blood pressure 6 and 24 h after dosing. Canadian Journal of Cardiology 1996; 12(11):1191-6.

131. Overlack A, Adamczak M, Bachmann W, Bonner G, Bretzel RG, Derichs R, et al. ACE-inhibition with perindopril in essential hypertensive patients with concomitant diseases. American Journal of Medicine 1994; 97(2):126-34.

132. Bonner G, Lederle RM, Scholze J, Stumpe KO. Therapeutic safety of perindopril in the treatment of mild hypertension with concomitant nephropathy. Arzneimittelforschung 1993; 43(8):852-5.

133. Middeke M, Krone W. Effects of perindopril on serum lipids in hypertensive patients with hyperlipidemia. Journal of Cardiovascular Pharmacology 1994; 23(4):629-31.

134. Overlack A, Kronig B, Stumpe KO. Clinical and functional course of COPD in hypertensive patients with concomitant chronic bronchitis and emphysema during treatment with an ace inhibitor, perindopril. Journal of Drug Development 1993; 6(1):5-9.

135. Stumpe KO, Overlack A. Angiotensin-converting enzyme inhibition in mild hypertension with concomitant diseases and therapies: an efficacy, safety, and compatibility study of novel design, the Perindopril Therapeutic Safety Study. American Journal of Medicine 1992; 92(4B):98S-101S.

136. Stumpe KO, Overlack A. A new trial of the efficacy, tolerability, and safety of angiotensin-converting enzyme inhibition in mild systemic hypertension with concomitant diseases and therapies. American Journal of Cardiology 1993; 71(17):32E-7E.

137. Reimann HJ, Muller M, Trinczek-Gartner H, Kirchhoff R, Kirchhoff G. ACE inhibition in hypertensive patients with concomitant NSAID therapy. Munchener Medizinische Wochenschrift 1995; 137(12):187-91.

138. Maclean D. Quinapril: a double-blind, placebo-controlled trial in essential hypertension. Angiology 1989; 40(4 Pt 2):370-81.

139. Yebes RB. A placebo-controlled, double-blind study to evaluate the efficacy of once daily quinapril in patients with mild to moderate hypertension. Philippine Journal of Internal Medicine 1993; 31(6):317-26.

140. Homuth V, Faulhaber H-D, Loose U, Loffler K, Luft FC. Usefulness of piretanide plus ramipril for systemic hypertension: A multicenter trial. American Journal of Cardiology 1993; 72(9):666-71.

141. Kostis JB. Double-blind study of ascending doses of ramipril in patients with mild to moderate hypertension. Advances in Therapy 1991; 8(1):6-17.

142. McCarron D, Reeves R, Levy B, Silberman H, Nedelman P, Mroczek W, et al. 24-Hour blood pressure profiles in hypertensive patients administered ramipril or placebo once daily: Magnitude and duration of antihypertensive effects. Clinical Cardiology 1991; 14(9):737-42.

143. Scholze J, Bauer B, Massaro J. Antihypertensive profiles with ascending dose combinations of ramipril and felodipine ER. Clinical and Experimental Hypertension 1999; 21(8):1447-62.

144. Trevisan R, Tiengo A. Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. American Journal of Hypertension 1995; 8(9):876-83.

145. Villamil AS, Cairns V, Witte PU, Bertolasi CA. A double-blind study to compare the efficacy, tolerance and safety of two doses of the angiotensin converting enzyme

inhibitor ramipril with placebo. American Journal of Cardiology 1987; 59(10):110D-4D.

146. Fairhurst GJ. A multicentre multidose study of the efficacy and safety of spirapril in mild-to-moderate essential hypertension. Blood Pressure 1994; Supplement. 2:77-80.

147. Guitard C, Alvisi V, Maibach E, Franck J, Cocco G, Boxho G, et al. Placebo-controlled comparison of spirapril at 6, 12 and 24 mg/day in mild to severe essential hypertension. Blood Pressure 1994; Supplement. 3(2):81-7.

148. Pittrow DB, Antlsperger A, Welzel D, Wambach G, Schardt W, Weidinger G. Evaluation of the efficacy and tolerability of a low-dose combination of isradipine and spirapril in the first-line treatment of mild to moderate essential hypertension. Cardiovascular Drugs & Therapy 1997; 11(5):619-27.

149. Lerch M, Weidmann P, Ho MP, Gerber P, Eckenberger P, Kaemmereit A, et al. Metabolic effects of temocapril in hypertensive patients with diabetes mellitus type 2. Journal of Cardiovascular Pharmacology 1999; 33(4):527-33.

150. De Bruijn JH, Orofiamma BA, Pauly NC. Efficacy and tolerance of trandolapril (0.5-2 mg) administered for 4 weeks in patients with mild-to-moderate hypertension. Journal of Cardiovascular Pharmacology 1994; 23 Suppl 4:S60-S64.

151. DeQuattro V, Lee D, Messerli F. Efficacy of combination therapy with trandolapril and verapamil sr in primary hypertension: a 4 x 4 trial design. Clinical and Experimental Hypertension 1997; 19(3):373-87.

152. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. American Journal of Hypertension 1997; 10(7 Pt 2):138S-45S.

153. Levine JH, Applegate WB. Trandolapril and verapamil slow release in the treatment of hypertension: A dose-response assessment with the use of a multifactorial trial design. Current Therapeutic Research, Clinical & Experimental 1997; 58(6):361-74.

154. Kohlmann JO, Jardim PC, Oigman W. Brazilian multicenter study on efficacy and tolerability of trandolapril in mild-to-moderate essential arterial hypertension. EMBATHE substudy with ambulatory blood pressure monitoring. Arquivos Brasileiros Cardiologia 1999; 72(5):547-57.

155. Schnaper HW. Dose-response relationship of ramipril in patients with mild-to-moderate hypertension. Journal of Cardiovascular Pharmacology 1991; 18 Suppl 2:S128-S130.

156. Mancia G, De Cesaris R, Fogari R, Lattuada S, Montemurro G, Palombo C, et al. Evaluation of the antihypertensive effect of once-a-day trandolapril by 24-hour

ambulatory blood pressure monitoring. American Journal of Cardiology 1992; 70(12):60D-6D.

157. Ravogli A, Omboni S, De Cesaris R, Fogari R, Lattuada S, Montemurro G, et al. Twenty-four-hour ambulatory blood pressure monitoring and antihypertensive treatment: focus on ACE inhibitors. Journal of Cardiovascular Pharmacology 1994;23 Suppl 1:S15-S19.

158. Mancia G, Agabiti-Rosei E, Benetti G, Calcagnini G, Campa PP, Carretta R, et al. Effects of verapamil SR, trandolapril, and their fixed combination on 24-h blood pressure: The Veratran Study. American Journal of Hypertension 1997; 10(5 I):492-9.

159. Burris JF. The effect of ramipril on ambulatory blood pressure: a multicenter trial. Journal of Cardiovascular Pharmacology 1991; 18 Suppl 2:S131-S133.

160. Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. American Journal of Hypertension 1998; 11(3 Pt 1):322-7.

161. New JP, Bilous RW, Walker M. Insulin sensitivity in hypertensive Type 2 diabetic patients after 1 and 19 days' treatment with trandolapril. Diabetic Medicine 2000; 17(2):134-40.

162. Scholze J, Zilles P, Compagnone D. Verapamil SR and trandolapril combination therapy in hypertension--a clinical trial of factorial design. German Hypertension Study Group. British Journal of Clinical Pharmacology 1998; 45(5):491-5.

163. Vaur L, Dubroca I, Dutrey-Dupagne C, Genes N, Chatellier G, Bouvier-d'Yoire M, et al. Superiority of home blood pressure measurements over office measurements for testing antihypertensive drugs. Blood Pressure Monitoring 1998; 3(2):107-14.

164. Weir MR, Gray JM, Paster R, Saunders E. Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. Hypertension 1995; 26(1):124-30.

165. Weir MR, Saunders E. Renin status does not predict the anti-hypertensive response to angiotensin-converting enzyme inhibition in African-Americans. Journal of Human Hypertension 1998; 12(3):189-94.

166. Deeks JJ, Higgins JPT, Altman DG, editors. Analysing and presenting results. In: Higgins, JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 8. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

167. World Health Organization. International Clinial Trials Registry Platform (ICTRP). [Online] 2007 [cited 2007 November 17]. Available from: URL: http://www.who.int/ictrp/en/

# 3 BLOOD PRESSURE LOWERING EFFICACY OF ANGIOTENSIN RECEPTOR BLOCKERS FOR PRIMARY HYPERTENSION[2]

## 3.1 Protocol

The protocol for this systematic review was first published in Issue 2, 2002 of the Cochrane Library [1] to outline the scientific methods that would be employed. The methodology was based on the Cochrane Reviewers' Handbook [2] and on a previous systematic review that assessed the blood pressure lowering efficacy of thiazide and loop diuretics [3].

### 3.1.1 Objectives

**Primary objective:**

- To quantify the dose-related systolic and/or diastolic blood pressure lowering efficacy of angiotensin receptor blockers (ARBs) versus placebo in the treatment of primary hypertension.

**Secondary objectives:**

- To determine the effects of ARBs on variability of blood pressure.
- To determine the effects of ARBs on pulse pressure.
- To quantify the dose-related effects of ARBs on heart rate.
- To quantify the dose-related effect of ARBs on withdrawals due to adverse effects.

### 3.1.2 Methodology

#### 3.1.2.1 Types of studies

Included studies must be RCTs and their design must meet the following criteria:

- double-blind
- random allocation to fixed dose ARB monotherapy group(s) and a parallel placebo control group
- duration of follow-up of at least three weeks

[2] A version of this chapter has been accepted for publication. Heran, B.S., Wong, M.M.Y., Heran I.K. and Wright, J.M. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension.

- office blood pressure measurements at baseline (following washout) and at one or more time points between 3 and 12 weeks post-treatment

#### 3.1.2.2 Types of participants

Participants must have an office baseline blood pressure of at least 140 mm Hg systolic and/or a diastolic blood pressure of at least 90 mm Hg. Patients must not have creatinine levels greater than 1.5 times the normal level, thereby excluding patients with secondary hypertension due to renal failure. Participants who were taking medications that affect blood pressure other than the study medications were excluded. Participants were not restricted by age, gender, baseline risk or any other co-morbid conditions.

#### 3.1.2.3 Types of interventions

Monotherapy with any angiotensin receptor blocker, including candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan, and KT3-671.

Trials in which titration to a higher dose based on blood pressure response were not eligible if the titration occurred before 3 weeks of treatment because dose-response relationships cannot be analyzed if patients within each randomized group are taking different doses. However, trials in which a response-dependent titration took place during or after the 3 to 12 week interval were eligible if pre-titration data were given. For forced titration trials, data from the lowest dose were extracted, provided this dose was given for a 3 to 12 week period.

#### 3.1.2.4 Types of outcome measures

**Primary:**

- Change from baseline of trough and/or peak systolic and diastolic blood pressure at 3 to 12 weeks, compared with placebo. If blood pressure measurements were available at more than one time within the accepted window, the weighted means of blood pressures taken in the 3 to 12 week range were used.

**Secondary:**

- Standard deviation of the change in blood pressure compared with placebo.
- Change in standard deviation of blood pressure compared with placebo.

- Change in pulse pressure compared with placebo.
- Change in heart rate compared with placebo.
- Number of patient withdrawals due to adverse effects compared with placebo.

### 3.1.3 Search strategy for identification of studies

To identify randomized, double-blind, placebo-controlled trials of angiotensin receptor blockers, Medline (1966-present), EMBASE (1988-present), Cochrane Central Register of Controlled Trials (CENTRAL), and bibliographic citations were searched. Previously published meta-analyses on dose-response of ARBs, as well as narrative reviews, were used to help identify references to trials. No language restrictions were applied.

A modified, expanded version of the standard search strategy of the hypertension review group was used to identify the relevant articles [4].

#### 3.1.3.1 Search strategy used for Medline

1. randomized controlled trial.pt
2. randomized controlled trial$.mp
3. controlled clinical trial.pt
4. controlled clinical trial$.mp
5. random allocation.mp
6. exp double-blind method/
7. double-blind.mp
8. exp single-blind method/
9. single-blind.mp
10. or/1-9
11. ANIMALS.sh. not HUMAN.sh.
12.10 not 11
13. clinical trial.pt
14. clinical trial$.mp
15. exp clinical trials/
16. (clin$ adj25 trial$).mp
17. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).mp

18. random$.mp
19. exp research design/
20. research design.mp
21. or/13-20
22. 21 not 11
23. 22 not 12
24. comparative stud$.mp
25. exp evaluation studies/
26. evaluation stud$.mp
27. follow-up stud$.mp
28. prospective stud$.mp
29. (control$ or prospectiv$ or volunteer$).mp
30. or/24-29
31. 30 not 11
32. 31 not (12 or 23)
33. 12 and 23 and 32
34. exp angiotensin II type I receptor blockers/
35. angiotensin receptor blocker$.mp.
36. angiotensin II receptor blocker$.mp.
37. angiotensin receptor antagonist$.mp.
38. angiotensin II receptor antagonist$.mp.
39. candesartan.mp.
40. eprosartan.mp.
41. irbesartan.mp.
42. exp losartan/
43. losartan.mp.
44. olmesartan.mp.
45. tasosartan.mp.
46. telmisartan.mp
47. valsartan.mp
48. KT3-671.mp.

49. or/34-48
50. exp hypertension/
51. hypertension.mp.
52. exp blood pressure/
53. blood pressure.mp.
54. or/50-53
55. 49 and 54
56. 33 and 55
57. placebo$.mp.
58. 56 and 57

#### 3.1.3.2 Search strategy used for EMBASE

1. randomi?ed controlled trial$.mp.
2. exp controlled clinical trials/
3. controlled clinical trial$.mp.
4. exp random allocation/
5. random allocation.mp.
6. double-blind.mp.
7. single-blind.mp.
8. or/1-7
9. exp animal/
10. 8 not 9
11. exp clinical trials/
12. clinical trial$.mp.
13. (clin$ adj25 trial$).mp.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
15. random$.mp.
16. exp research design/
17. research design.mp.
18. or/11-17
19. 18 not 9

20. 19 not 10
21. exp comparative study/
22. comparative stud$.mp.
23. exp evaluation studies/
24. evaluation stud$.mp.
25. exp follow up studies/
26. follow up stud$.mp.
27. prospective stud$.mp.
28. (control$ or prospectiv$ or volunteer$).mp.
29. or/21-28
30. 29 not 9
31. 30 not (10 or 20)
32. 10 and 20 and 31
33. exp angiotensin II type 1 receptor blockers/
34. angiotensin receptor blocker$.mp.
35. angiotensin II receptor blocker$.mp.
36. angiotensin receptor antagonist$.mp.
37. angiotensin II receptor antagonist$.mp.
38. candesartan.mp.
39. eprosartan.mp.
40. irbesartan.mp.
41. losartan.mp.
42. olmesartan.mp.
43. tasosartan.mp.
44. telmisartan.mp
45. valsartan.mp
46. KT3-671.mp.
47. or/33-46
48. exp hypertension/
49. hypertension.mp.
50. exp blood pressure/

51. blood pressure.mp.

52. or/48-51

53. 47 and 52

54. 32 and 53

55. placebo$.mp.

56. 54 and 55

### 3.1.4 Study selection

The databases listed above were searched using the updated search strategy to identify citations with potential relevance. The initial screen of these abstracts excluded articles whose titles and/or abstracts were clearly irrelevant. The full text of remaining articles were then retrieved (and translated into English where required) to assess whether or not the trials met the pre-specified inclusion criteria. The bibliographies of pertinent articles, reviews and texts were searched for additional citations. Two independent reviewers assessed the eligibility of the trials using a trial selection form (Appendix I). A third reviewer resolved discrepancies. Trials with more than one publication were counted only once.

### 3.1.5 Data extraction

Data were extracted independently by two reviewers using a standard form (Appendix II) and then cross-checked. If data were presented numerically (in tables or text) and graphically (in figures), the numeric data were preferred because of possible measurement error when estimating from graphs. All numeric calculations and extractions from graphs or figures were confirmed by a second reviewer.

The position of the patient during blood pressure measurement may affect the blood pressure lowering effect. However, in order not to lose valuable data, if only one position was reported, data from that position were extracted. When blood pressure measurement data are available in more than one position, data were extracted in accordance with the following order of preference: 1) sitting; 2) standing; and 3) supine.

In the case of missing information in the included studies, investigators were contacted (by email, letter and/or fax) to obtain the missing information.

In the case of missing values for standard deviation of the change in blood

pressure or heart rate, the standard deviation was imputed based on the information in the same trial or from other trials using the same dose. The following hierarchy (listed from high to low preference) was used to impute standard deviation values:

1. Pooled standard deviation calculated either from the t-statistic corresponding to an exact p-value reported or from the 95% confidence interval of the mean difference between treatment group and placebo.
2. Standard deviation of change in blood pressure/heart rate from a different position than that of the blood pressure data/heart rate used.
3. Standard deviation of blood pressure/heart rate at the end of treatment.
4. Standard deviation of blood pressure/heart rate at the end of treatment measured from a different position than that of the blood pressure/heart rate data used.
5. Standard deviation of blood pressure/heart rate at baseline (except if this measure was used for entry criteria).
6. Weighted mean standard deviation of change in blood pressure/heart rate from other trials using the same class of drug (at any dose).

### 3.1.6 Quality assessment

The quality of all included trials was assessed by two independent reviewers using the following two approaches that are commonly utilized in systematic reviews.

#### 3.1.6.1 Cochrane assessment of allocation sequence concealment

The Cochrane Collaboration judges the quality of a study on the method of allocation concealment [5]. Each trial in the systematic review is assigned a grade of A, B, C, or D:

**Grade A: Adequate**

- Some approaches that are adequate include: centralized (eg. central office unaware of subject characteristics) or pharmacy-controlled randomization; pre-numbered or coded identical containers which are administered serially to participants; on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; sequentially numbered, sealed, opaque envelopes.

**Grade B: Unclear**

- Adequacy should be considered unclear when the allocation concealment approach is not reported in the study, for example: simply stating that a list or table was used; only specifying that sealed envelopes were used or reporting an apparently adequate concealment scheme along with other details that leads the reviewer to be suspicious.

**Grade C: Inadequate**

- Some approaches that are clearly inadequate include: alternation; the use of case record numbers; dates of birth; or any procedure that is transparent before allocation, such as an open list of random numbers.

**Grade D: Allocation concealment not used**

- Allocation concealment was not used to assess validity.

#### 3.1.6.2 Jadad quality scale

A simple 5-point scoring system where a score of 0-2 reflects low quality, a score of 3-4 indicates moderate quality and a score of 5 represents a high quality study [6]. It is summarised as follows:

- Was the study described as randomised? (1=yes; 0=no)
- Was the study described as double-blind? (1=yes; 0=no)
- Was there a description of withdrawals and dropouts? (1=yes; 0=no)
- Was the method of randomisation well described and appropriate? (1=yes; 0=no)
- Was the method of double-blinding well described and appropriate? (1=yes; 0=no)
- Deduct 1 point if methods for randomisation were inappropriate.
- Deduct 1 point if methods for blinding were inappropriate.

### 3.1.7 Data analysis and statistical considerations

Data synthesis and analyses was done using the Cochrane Review Manager software, RevMan 4.2.8. Data for changes from baseline in blood pressure and heart rate were combined using a weighted mean difference method. The withdrawals due to adverse effects were analyzed using relative risk, risk difference, and number needed to harm.

When possible, direct and indirect comparisons of effect sizes between doses

were performed for each ARB drug. In the direct method, only trials that randomized participants to different doses were included in the analysis. In the indirect method, an "adjusted indirect comparison" and the associated standard error were calculated using the method described by Bucher et al. (1997) [7,8].

A p value less than 0.05 ($p < 0.05$) was considered statistically significant for all comparisons. If there was statistically significant heterogeneity associated with an effect estimate, a random effects model was applied. This model provides a more conservative statistical comparison of the difference between ARB treatment and placebo because a confidence interval around the effect estimate is wider than a confidence interval around a fixed effect estimate. If a statistically significant difference was still present using the random effects model, the fixed effect pooled estimate and confidence interval were reported because of the tendency of smaller trials, which are more susceptible to publication bias, to be overweighted with a random effects analysis.

When possible, subgroup analyses were used to examine the results for specific categories of participants. Possible subgroup analyses included:

- Race: black, white, other
- Age: children, adults, older people
- Baseline severity of hypertension: mild, moderate, severe

The robustness of the results was tested using several sensitivity analyses, including:

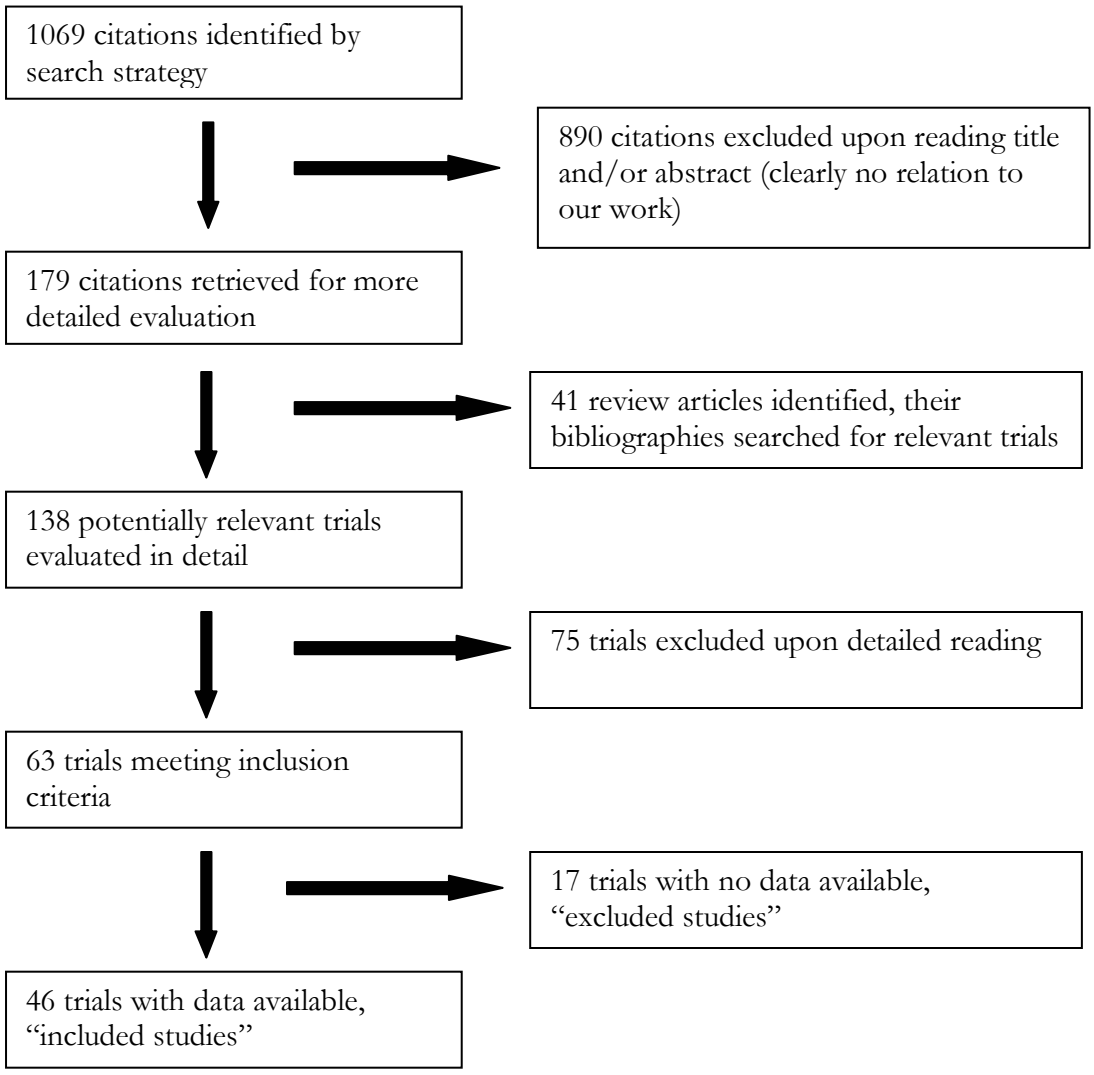
- Trials of high quality versus poor quality.
- Trials that are industry-sponsored versus non-industry sponsored.
- Trials that assess drug as primary drug of investigation versus trials that assess drug as comparator.
- Trials with blood pressure data measured in the sitting position versus other measurement positions.
- Trials with published standard deviations of blood pressure change versus imputed standard deviations.

## 3.2 Results

### 3.2.1 Search findings

The search strategy identified 1069 citations, of which only 46 (4.3%) trials met the inclusion criteria and had extractable data to evaluate the dose-related blood pressure lowering efficacy of 9 ARBs (Figure 3.1). Seventy five studies were excluded because they did not meet the pre-specified inclusion criteria. An additional seventeen trials met the inclusion criteria but did not have extractable and therefore were excluded.

**Figure 3.1: QUOROM flow diagram**



#### 3.2.1.1 Characteristics of excluded studies

Seventeen studies that met the inclusion criteria were excluded from this review. Some of the reasons for exclusion were failure to report adequate blood pressure data, crossover trials that did not report pre-crossover data, parallel group trials with a forced titration schedule and trials in which patients were titrated to a pre-specified blood pressure response were also excluded. Reasons for excluding each trial are listed in Table 3.1.

**Table 3.1: Reasons for exclusion of trials that met inclusion criteria**

| Study ID | Reason for exclusion |
|---|---|
| Asmar 2000 [9]<br>Duplicate publication: Lacourciere 1999 [10] | Parallel group trial with 8-week treatment period, forced titration at 4 weeks. BP data for placebo group not reported at 4 weeks (candesartan 8 mg/day vs. placebo). |
| Asmar 2001 [11] | Crossover trial with no pre-crossover data reported for first 4 weeks of treatment (telmisartan 40 mg/day vs. placebo). |
| ABC Trial 2000 [12] | Parallel group trial in black patients with 12-week treatment period, titration in non-responders every 4 weeks. Pre-titration data not reported (candesartan 16 mg/day vs. placebo). |
| Bakris 2002 [13] | Parallel group trial with 8-week treatment period, forced titration at 4 weeks. Pre-titration data not reported (losartan 50 mg/day vs. enalapril 10 mg/day vs. placebo). |
| Fagard 2001 [14] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (losartan 50 mg/day vs. enalapril 20 mg/day vs. placebo). |
| Fridman 1999 [15]<br>Duplicate publication: Fridman 2000 [16] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (candesartan 16 mg/day vs. placebo). |

| Study ID | Reason for exclusion |
|---|---|
| Hedner 1999 [17] | Parallel group trial with 13-week treatment period, including 9-week dose titration phase followed by 4-week maintenance phase. Pre-titration data not reported (eprosartan 400 mg once daily vs. eprosartan 200 mg twice daily vs. placebo). |
| Koh 2004 [18] Duplicate publication: Koh 2004 [19] | Parallel group trial with 8-week treatment period. Time and position of BP measurement not reported. BP measurement device also not reported. (losartan 100 mg/day vs. irbesartan 300 mg/day vs. candesartan 16 mg/day vs. placebo). |
| Lacourciere 1998 [20] | Parallel group trial with 12-week treatment period, titration in non-responders every 4 weeks. Pre-titration data not reported (telmisartan 40 mg/day vs. placebo). |
| Lacourciere 1999 [21] | Parallel group trial with 8-week treatment period. BP data for placebo group not reported (telmisartan 80 mg/day vs. lisinopril 20 mg/day vs. placebo). |
| Marino 1999 [22] | Parallel group trial with 4-week treatment period. BP data reported as 24 h area under curve (irbesartan 300 mg/day vs. placebo). |
| McInnes 1997 [23] | Parallel group trial with 12-week treatment period, titration in non-responders at 6 weeks. Pre-titration data not reported (candesartan 8 mg/day vs. placebo). |
| Neutel 1997 [24] | Parallel group trial with 8-week treatment period. Only ambulatory BP monitoring data reported (valsartan 20, 80, 160, 320 mg/day vs. placebo). |
| Neutel 2000 [25] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (valsartan 80 mg/day vs. placebo). |
| Petrov 2001 [26] | Crossover trial with no pre-crossover data reported for first 6 weeks of treatment (losartan 50 mg/day vs. enalapril 20 mg/day vs. placebo). |

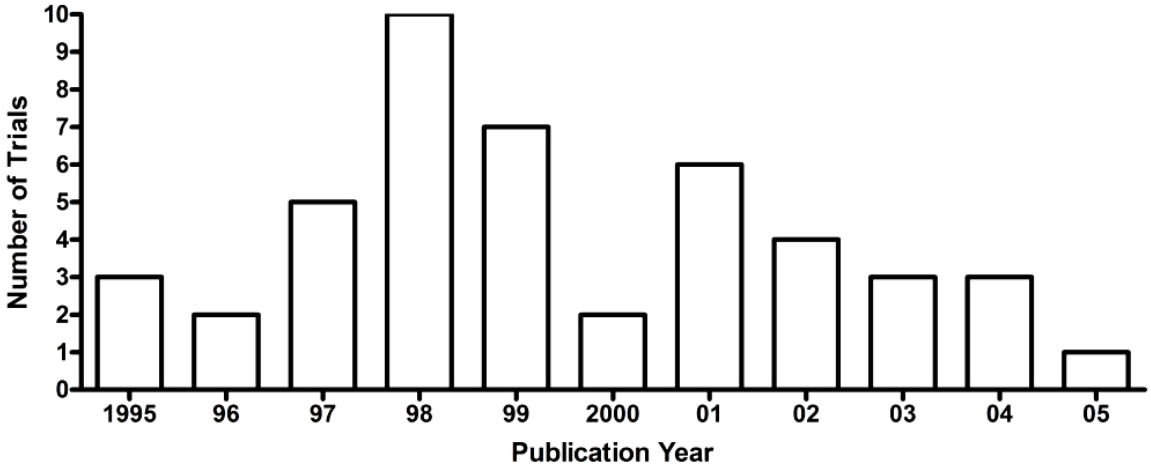
| Study ID | Reason for exclusion |
|---|---|
| Zanchetti 2001 [27] | Parallel group trial with 8-week treatment period, titration in non-responders at 4 weeks. Pre-titration data not reported (candesartan 4 mg/day vs. enalapril 10 mg/day vs. placebo). |
| Zuschke 1999 [28] | Parallel group trial with 8-week treatment period, forced titration at 4 weeks. Pre-titration data not reported (candesartan 16 mg once daily vs. candesartan 8 mg twice daily vs. placebo). |

#### 3.2.1.2 Overview of included studies

All 46 included studies were published in English. Forty-one (89%) of the included studies were industry-sponsored while the remaining 5 (11%) did not report the source of funding. Six duplicate publications of 3 included trials were identified. Thirty four (74%) of the included studies randomized patients to fixed-dose monotherapy during double-blind treatment, 2 (4%) were forced-titration studies and 10 (22%) were titration to blood pressure response at pre-specified intervals during the double-blind treatment phase. Only the pre-titration blood pressure data were used in the analysis of the latter 12 studies.

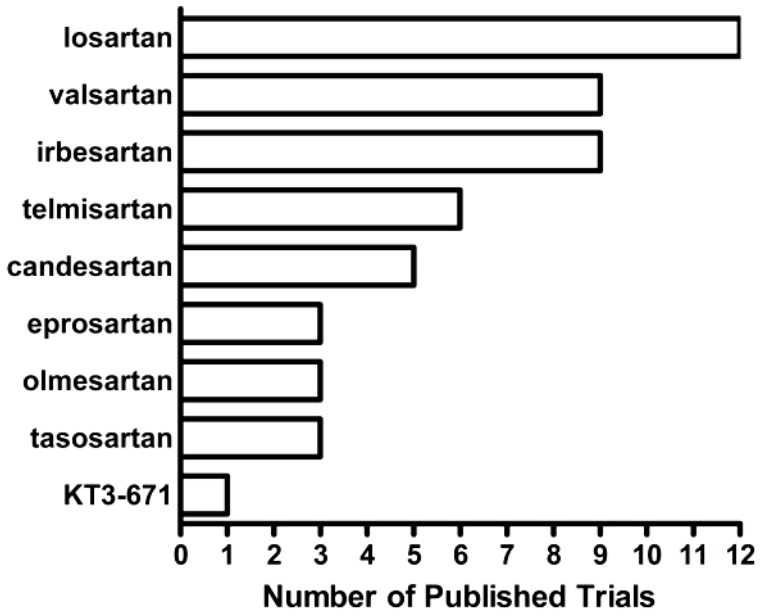
Trials evaluating the antihypertensive efficacy of ARB monotherapy using office blood pressure measurements were first published in 1995 (Figure 3.2). There was an increase in the number of published studies through the 1990s, peaking at 10 trials published in 1998. After 1998, the number of trials published each year declined.

**Figure 3.2: Number of included studies evaluating ARBs according to publication year**




Losartan is the most extensively studied ARB with 12 published studies investigating the antihypertensive efficacy of daily doses ranging from 10 to 150 mg daily (Figure 3.3).

**Figure 3.3: Number of included studies evaluating ARBs according to ARB studied**




Tables 3.2 - 3.10 summarize the characteristics of each included study. Each study was assigned a unique identifier consisting of the surname of the first author followed by the year of publication.

**Table 3.2: Characteristics of included studies evaluating candesartan**

| Study | Study Description |
|---|---|
| Andersson 1998 [29] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 82 (47 males, 35 females); mean age 60 (11) years; baseline sitting SBP 169 (14) mm Hg, DBP 102 (5) mm Hg; candesartan 16 mg: n 84 (56 males, 28 females); mean age 59 (10) years; baseline sitting SBP 168 (15) mm Hg, DBP 103 (5) mm Hg; losartan 50 mg: n = 83 (47 males, 36 females); mean age 59 (9) years; baseline sitting SBP 168 (16) mm Hg, DBP 104 (5) mm Hg; placebo: n = 85 (38 males, 47 females); mean age 60(10) years; baseline sitting SBP 170 (14) mm Hg, DBP 103 (5) mm Hg<br><br>**Interventions:** Candesartan 8 mg once daily; candesartan 16 mg once daily; losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using fully automatic device (Omron HEM-705CP); peak sitting SBP/DBP using fully automatic device (Omron HEM-705CP); WDAE<br><br>**Funding source:** Astra Hassle AB, Sweden<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported, baseline SD reported; imputed endpoint SD for SD of change; BP data from Table II, p. 55 |
| Farsang 2001 [30] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 5<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 85 (63 males, 22 females); mean age 51 (11) years: baseline sitting SBP 161.8 (14.1) mm Hg, DBP 102.1 (4.6) mm Hg; standing SBP 159.0 (18.4) mm Hg, DBP 104.1 (9.8) mm Hg; placebo: n = 83 (54 males, 29 females); mean age 52 (10) years; baseline sitting SBP 161.5 (16.3) mm Hg, DBP 102.1 (5.2) mm Hg; standing SBP 157.5 (18.7) mm Hg, DBP 102.5 (8.9) mm Hg<br><br>**Interventions:** Candesartan 8 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough |

| Study | Study Description |
|---|---|
| | sitting SBP/DBP using fully automatic device (Omron HEM-705CP); mean change from baseline in trough standing SBP/DBP using fully automatic device (Omron HEM-705CP); WDAE<br><br>**Funding source:** Astra Hassle AB, Sweden<br><br>**Notes:** BP change and 95% CI of change reported, endpoint BP and SD not reported, baseline SD reported; 95% CI of change values are not appropriate; imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from Figure 1a, p. 20 |
| Fogari 2001<br>[31] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 12 weeks total, titration-to-response after 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Postmenopausal women (51-60 years old) with DBP 91-105 mm Hg and SBP < 180 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 29; mean age 55.1 (2.0) years; baseline SBP 159.8 (12.3) mm Hg, DBP 100.5 (7.2) mm Hg, HR 76.8 (8.9) bpm; irbesartan 150 mg: n = 28; mean age 55.2 (2.3) years; baseline SBP 160.6 (13.0) mm Hg, DBP 100.9 (5.9) mm Hg, HR 75.9 (8.8) bpm; losartan 50 mg: n = 28; mean age 54.7 (2.3) years; baseline SBP 160.2 (12.1) mm Hg, DBP 99.8 (7.1) mm Hg, HR 76.1 (8.6) bpm; valsartan 80 mg: n = 30; mean age 54.8 (2.2) years; baseline SBP 161.2 (11.9) mm Hg, DBP 101.3 (6.7) mm Hg, HR 77.2 (9.2) bpm; placebo: n = 25; mean age 55.1(2.1) years; baseline SBP 159.7 (11.5) mm Hg, DBP 100.6 (6.1) mm Hg, HR 75.7 (9.1) bpm<br><br>**Interventions:** Candesartan 8 mg once daily; irbesartan 150 mg once daily; losartan 50 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using standard mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** not reported<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change not reported, week 6 BP and SD reported, imputed 6-week SD for SD of change; BP data from Table II, p. 73 |
| Meineke 1997<br>[32] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3 |

| Study | Study Description |
|---|---|
| | **Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** All candesartan groups: n = 185 (129 males, 56 females); mean age 53 years; candesartan 2 mg: baseline sitting SBP 151.7 mm Hg, DBP 102.4 mm Hg; candesartan 4 mg: baseline sitting SBP 154.9 mm Hg, DBP 104.0 mm Hg; candesartan 8 mg: baseline sitting SBP 152.1 mm Hg, DBP 102.0 mm Hg; candesartan 12 mg: baseline sitting SBP 153.4 mm Hg, DBP 103.4 mm Hg; candesartan 16 mg: baseline sitting SBP 152.3 mm Hg, DBP 102.4 mm Hg; placebo: n = 39; baseline sitting SBP 154.6 mm Hg, DBP 103.2 mm Hg<br><br>**Interventions:** Candesartan 2 mg once daily; candesartan 4 mg once daily; candesartan 8 mg once daily; candesartan 12 mg once daily; candesartan 16 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP<br><br>**Funding source:** Takeda Euro R&D Centre<br><br>**Notes:** BP and SD of change not reported, endpoint BP reported, endpoint SD not reported, baseline SD not reported; imputed overall trial mean SBP/DBP SD of change; BP data from Table 2, p. 225; BP measurement device not reported |
| Reif 1998<br><br>[33] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Candesartan 2 mg: n = 59 (29 males, 30 females); mean age 54 (10) years; baseline sitting SBP 152 (12) mm Hg, DBP 99 (4) mm Hg; candesartan 4 mg: n = 63 (44 males, 19 females); mean age 55 (11) years; baseline sitting SBP 152 (17) mm Hg, DBP 100 (5) mm Hg; candesartan 8 mg: n = 60 (34 males, 26 females); mean age 55 (11) years; baseline sitting SBP 154 (17) mm Hg, DBP 101 (6) mm Hg; candesartan 16 mg: n = 60 (38 males, 22 females); mean age 55 (11) years; baseline sitting SBP 153 (18) mm Hg, DBP 100 (5) mm Hg; candesartan 32 mg: n = 59 (41 males, 18 females); mean age 55 (12) years; baseline sitting SBP 152 (17) mm Hg, DBP 100 (5) mm Hg; placebo: n = 64 (46 males, 18 females); mean age 55 (12) years; baseline sitting SBP 154 (13) mm Hg, DBP 101 (5) mm Hg<br><br>**Interventions:** Candesartan 2 mg once daily; candesartan 4 mg once daily; |

| Study | Study Description |
|---|---|
| | candesartan 8 mg once daily; candesartan 16 mg once daily; candesartan 32 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Least squares mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Astra Merck Inc.<br><br>**Notes:** BP change and 95% CI of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD of change from 95% CI of change; BP data from Table II, p. 962 |

**Table 3.3: Characteristics of included studies evaluating eprosartan**

| Study | Study Description |
|---|---|
| Gradman 1999<br><br>[34] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg on 3 consecutive weekly visits before end of run-in, with no more than 12 mm Hg difference in DBP between 3 visits, and difference between means at last 2 visits could not exceed 8 mm Hg<br><br>**Participants:** Eprosartan 600 mg: n = 123 (71 males, 52 females); mean age 54.0 (11.1) years: baseline sitting SBP 149.3 (13.3) mm Hg, DBP 100.4 (4.4) mm Hg, HR 73.2 (7.8) bpm; placebo: n = 120 (76 males, 44 females); mean age 53.3 (9.9) years; baseline sitting SBP 151.3 (14.2) mm Hg, DBP 101.2 (4.4) mm Hg, HR 73.1 (7.7) bpm<br><br>**Interventions:** Eprosartan 600 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Least-squares mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; Least-squares mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; Least-squares mean change from baseline in trough sitting HR; Least-squares mean change from baseline in trough standing HR; WDAE<br><br>**Funding source:** SmithKline Beecham Pharma<br><br>**Notes:** BP and SE of change reported, endpoint BP and SD not reported; |

| Study | Study Description |
|---|---|
| | calculated SD of change from N and SE of change; BP data from text, p. 445 and p.446 and Figure 1, p. 447 |
| Oparil 1999 [35] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg and difference between their average sitting DBP values for last 2 visits of placebo run-in period did not exceed 12 mm Hg<br><br>**Participants:** Eprosartan: n = 46 (27 males, 19 females); baseline sitting SBP 153.1 (14.9) mm Hg, DBP 101.5 (4.1) mm Hg, HR 75.9 (7.5) bpm; enalapril 20 mg: n = 45 (23 males, 22 females); baseline sitting SBP 154.6 (14.1) mm Hg, DBP 100.9 (4.7) mm Hg, HR 74.8 (9.4) bpm; placebo: n = 45 (21 males, 24 females); baseline sitting SBP 154.1 (14.1) mm Hg, DBP 99.8 (4.0) mm Hg, HR 74.4 (8.1) bpm<br><br>**Interventions:** Eprosartan 300 mg twice (200 mg for first 3 days) daily; enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in sitting DBP; WDAE<br><br>**Funding source:** SmithKline Beecham Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported, DBP data from text, p. 8 and Figure 3, p. 10; time of BP measurement not reported; BP measurement device not reported |
| Punzi 2004 [36] | **Design:** Placebo run-in period: 3-5 weeks; Treatment duration: 13 weeks total, 6-week titration phase (week 0-6), 3-week monotherapy maintenance phase, and 4-week combination therapy phase<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Patients with isolated systolic hypertension, defined as mean sitting SBP $\geq$ 160 mm Hg and mean sitting DBP < 90 mm Hg at 3 consecutive run-in visits<br><br>**Participants:** Eprosartan 600 mg: n = 148 (67 males, 81 females); mean age 69.8 (7.3) years; baseline sitting SBP 171 (9.7) mm Hg, DBP 83.4 (4.9) mm Hg, HR 73.0 (7.3) bpm; placebo: n = 135 (60 males, 75 females); mean age 70.4 (7.0) years; baseline sitting SBP 170 (9.3) mm Hg, DBP 82.7 (5.8) mm |

| Study | Study Description |
|---|---|
| | Hg, HR 74.2 (8.1) bpm<br><br>**Interventions:** Eprosartan 600 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP using mercury sphygmomanometer<br><br>**Funding source:** SmithKline Beecham Pharma<br><br>**Notes:** Used week 3 SBP data only; BP change reported, SE of change reported, endpoint BP and SD not reported, baseline SD reported but not appropriate; calculated SD from SE and N, SBP data from Figure 2, p. 658 |
| White 2001<br><br>[37] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg on 2 consecutive visits with no more than 8 mm Hg difference in DBP between 2 visits<br><br>**Participants:** Eprosartan 600 mg: n = 59 (40 males, 19 females); mean age 54 (9) years; baseline sitting SBP 152 (12) mm Hg, DBP 100 (9) mm Hg; eprosartan 1200 mg: n = 63 (42 males, 21 females); mean age = 55 (10) years; baseline sitting SBP 154 (13) mm Hg, DBP 101 (9) mm Hg; placebo: n = 55 (39 males, 16 females); mean age 54 (9) years; baseline sitting SBP 152 (20) mm Hg, DBP 100 (10) mm Hg<br><br>**Interventions:** Eprosartan 600 mg once daily; eprosartan 1200 mg once daily; Placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP; WDAE<br><br>**Funding source:** SmithKline Beecham, Solvay Pharma<br><br>**Notes:** BP and SE of change reported, endpoint BP and SD not reported; calculated SD of change from N and SE of change; BP data from text, p. 1250; BP measurement device not reported |

**Table 3.4: Characteristics of included studies evaluating irbesartan**

| Study | Study Description |
|---|---|
| Benetos 2000<br>[38] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 3<br>**Inclusion criteria:** Mean supine DBP 100-114 mm Hg<br>**Participants:** Irbesartan 150 mg: n = 28 (22 males, 6 females); mean age 49 (5.3) years; baseline supine SBP 170.9 (16.1) mm Hg, DBP 106.7 (6.4) mm Hg; placebo: n = 27 (18 males, 9 females); mean age 54 (5.2) years; baseline supine SBP 164.2 (14.5) mm Hg, DBP 103.5 (3.0) mm Hg<br>**Interventions:** Irbesartan 150 mg once daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using Dinamap 845 oscillometric recorder; WDAE<br>**Funding source:** INSERM and Sanofi Research<br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table 1, p. 11 |
| Fogari 1997<br>[39] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br>**Quality:** Cochrane method = B; Jadad score = 4<br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg<br>**Participants:** Irbesartan 75 mg once daily: n = 55 (37 males, 18 females); mean age 56.7 (10.4) years; baseline sitting SBP 157.0 (13.4) mm Hg, DBP 101.4 (5.2) mm Hg; irbesartan 150 mg once daily: n = 53 (32 males, 21 females); mean age 54.6 (11.7) years; baseline sitting SBP 158.9 (13.8) mm Hg, DBP 101.0 (5.1) mm Hg; irbesartan 75 mg twice daily: n = 57 (36 males, 21 females); mean age 54.1 (10.6) years; baseline sitting SBP 156.0 (12.8) mm Hg, DBP 106.7 (4.5) mm Hg; placebo: n = 50 (36 males, 14 females); mean age 53.3 (11.3) years; baseline sitting SBP 158.3 (13.4) mm Hg, DBP 101.5 (5.0) mm Hg<br>**Interventions:** Irbesartan 75 mg once daily; irbesartan 150 mg once daily; irbesartan 75 mg twice daily; placebo<br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE |

| Study | Study Description |
|---|---|
| | **Funding source:** Bristol-Myers Squibb and Sanofi<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table 2, p. 1515 |
| Fogari 2001<br>[31] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 12 weeks total, titration-to-response after 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Postmenopausal women (51-60 years old) with DBP 91-105 mm Hg and SBP < 180 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 29; mean age 55.1 (2.0) years; baseline SBP 159.8 (12.3) mm Hg, DBP 100.5 (7.2) mm Hg, HR 76.8 (8.9) bpm; irbesartan 150 mg: n = 28; mean age 55.2 (2.3) years; baseline SBP 160.6 (13.0) mm Hg, DBP 100.9 (5.9) mm Hg, HR 75.9 (8.8) bpm; losartan 50 mg: n = 28; mean age 54.7 (2.3) years; baseline SBP 160.2 (12.1) mm Hg, DBP 99.8 (7.1) mm Hg, HR 76.1 (8.6) bpm; valsartan 80 mg: n = 30; mean age 54.8 (2.2) years; baseline SBP 161.2 (11.9) mm Hg, DBP 101.3 (6.7) mm Hg, HR 77.2 (9.2) bpm; placebo: n = 25; mean age 55.1(2.1) years; baseline SBP 159.7 (11.5) mm Hg, DBP 100.6 (6.1) mm Hg, HR 75.7 (9.1) bpm<br><br>**Interventions:** Candesartan 8 mg once daily; irbesartan 150 mg once daily; losartan 50 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using standard mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** not reported<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change not reported, week 6 BP and SD reported, imputed 6-week SD for SD of change; BP data from Table II, p. 73 |
| Gradman 2005<br>[40] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg<br><br>**Participants:** Irbesartan 150 mg: n = 134 (66 males, 68 females); mean age 56.1 (11.8) years; baseline sitting SBP 152.8 (11.2) mm Hg, DBP 99.4 (4.0) mm Hg, HR 72.9 (7.9) bpm; placebo: n = 131 (64 males, 67 females); mean |

| Study | Study Description |
|---|---|
| | age 57.1 (12.0) years; baseline sitting SBP 152.3 (12.1) mm Hg, DBP 98.9 (3.3) mm Hg, HR 72.8 (9.2) bpm<br><br>**Interventions:** Irbesartan 150 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using standard mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** Novartis<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change not reported, week 6 BP and SD reported, imputed 6-week SD for SD of change; BP data from Table II, p. 73 |
| Guthrie 1998<br>[41] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 12-weeks total, 6-week fixed dose therapy, then titrated to response at week 6<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings not differing by more than 8 mm Hg<br><br>**Participants:** Irbesartan 75 mg: n = 104 (71 males, 33 females); mean age 53 years; baseline sitting SBP 148.9 (14.2) mm Hg, DBP 100.6 (4.4) mm Hg, HR 73 (9) bpm; irbesartan 150 mg: n = 98 (62 males, 36 females); mean age 53 years; baseline sitting SBP 147.8 (12.9) mm Hg, DBP 99.5 (4.0) mm Hg, HR 72 (8) bpm; placebo: n = 117 (80 males, 37 females); mean age = 53 years; baseline sitting SBP 148.0 (14.2) mm Hg, DBP 99.9 (3.8) mm Hg, HR 72 (9) bpm<br><br>**Interventions:** Irbesartan 75 mg once daily; irbesartan 150 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** Used week 6 BP data only; BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table II, p. 222 |
| Kassler-Taub 1998<br>[42] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings |

| Study | Study Description |
|---|---|
| | not differing by more than 8 mm Hg<br><br>**Participants:** Irbesartan 150 mg: n = 142 (77 males, 65 females); mean age 53.1 (10.5) years; baseline sitting SBP 155.3 (16.2) mm Hg, DBP 101.1 (4.6) mm Hg; irbesartan 300 mg: n = 140 (80 males, 60 females); mean age 55.6 (10.4) years; baseline sitting SBP 155.4 (16.0) mm Hg, DBP 100.4 (4.5) mm Hg; losartan 100 mg: n = 138 (69 males, 69 females); mean age 55.0 (10.7) years; baseline sitting SBP 153.3 (15.5) mm Hg, DBP 100.6 (4.4) mm Hg; placebo: n = 147 (90 males, 57 females); mean age 53.8 (9.6) years; baseline sitting SBP 152.4 (14.7) mm Hg, DBP 100.3 (4.3) mm Hg<br><br>**Interventions:** Irbesartan 150 mg once daily; irbesartan 300 mg once daily; losartan 100 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; baseline SD not reported, calculated SD from N and SE; BP data from Table 2, p. 448 |
| Kochar 1999<br>[43] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings not differing by more than 8 mm Hg<br><br>**Participants:** All patients: n = 683 (444 males, 239 females); mean age 55.0 (10.5) years; baseline sitting SBP 151 (14.7) mm Hg, DBP 100 (4.2) mm Hg<br><br>**Interventions:** Irbesartan 37.5 mg once daily; irbesartan 100 mg once daily; irbesartan 300 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; baseline SD reported; BP data from Table 2, p. 801 |
| Pool 1998 (study 1)<br>[44] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks |

| Study | Study Description |
|---|---|
| | **Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings not differing by more than 8 mm Hg<br><br>**Participants:** All patients: n = 570 (382 males, 188 females); mean age 54.2 (10.3) years; baseline sitting SBP 152.9 (14.4) mm Hg, DBP 101.0 (4.3) mm Hg<br><br>**Interventions:** Irbesartan 50 mg once daily; irbesartan 100 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in peak sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table 2, p. 465 |
| Pool 1998 (study 2) [44] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings not differing by more than 8 mm Hg<br><br>**Participants:** All patients: n = 319 (220 males, 99 females); mean age 52.8 (10.2) years; baseline sitting SBP 149.8 (13.6) mm Hg, DBP 100.7 (4.2) mm Hg<br><br>**Interventions:** Irbesartan 100 mg once daily; irbesartan 200 mg once daily; irbesartan 300 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; mean change from baseline in peak sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from |

| Study | Study Description |
|---|---|
| | Table 2, p. 465 |

**Table 3.5: Characteristics of included studies evaluating losartan**

| Study | Study Description |
|---|---|
| Andersson 1998 [29] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 82 (47 males, 35 females); mean age 60 (11) years; baseline sitting SBP 169 (14) mm Hg, DBP 102 (5) mm Hg; candesartan 16 mg: n 84 (56 males, 28 females); mean age 59 (10) years; baseline sitting SBP 168 (15) mm Hg, DBP 103 (5) mm Hg; losartan 50 mg: n = 83 (47 males, 36 females); mean age 59 (9) years; baseline sitting SBP 168 (16) mm Hg, DBP 104 (5) mm Hg; placebo: n = 85 (38 males, 47 females); mean age 60(10) years; baseline sitting SBP 170 (14) mm Hg, DBP 103 (5) mm Hg<br><br>**Interventions:** Candesartan 8 mg once daily; candesartan 16 mg once daily; losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using fully automatic device (Omron HEM-705CP); peak sitting SBP/DBP using fully automatic device (Omron HEM-705CP); WDAE<br><br>**Funding source:** Astra Hassle AB, Sweden<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported, baseline SD reported; imputed endpoint SD for SD of change; BP data from Table II, p. 55 |
| Cushman 2002 [45] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 12 weeks total, 4 weeks at initial fixed dose of losartan monotherapy (week 0-4), non-responders titrated to losartan 50 mg/HCTZ 12.5 mg combination after 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Patients with isolated systolic hypertension, defined as mean trough sitting SBP 140-200 mm Hg and mean trough sitting DBP 70-89 mm Hg |

| Study | Study Description |
|---|---|
| | **Participants:** Losartan 50 mg: n = 157 (71 males, 86 females); mean age 66.9 (9.7) years; baseline sitting SBP 165.3 (12.1) mm Hg, DBP 83.6 (5.4) mm Hg, HR 73.5 (8.7) bpm; placebo: n = 151 (72 males, 79 females); mean age 66.7 (9.5) years; baseline sitting SBP 166.1 (12.1) mm Hg, DBP 84.4 (5.6) mm Hg, HR 73.7 (8.3) bpm<br><br>**Interventions:** Losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP using mercury sphygmomanometer<br><br>**Funding source:** Merck & Co.<br><br>**Notes:** Endpoint BP and SD not reported, baseline SD reported but not appropriate; imputed overall trial mean SBP SD of change; BP data from text, p. 105; WDAE reported at endpoint but not at week 4 |
| Flack 2001<br>[46] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks total, 4 weeks at initial fixed dose of losartan 50 mg monotherapy or losartan 50 mg/HCTZ 0 mg combination (week 0-4), titration-to-response every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-109 mm Hg<br><br>**Participants:** Losartan 50 mg monotherapy: n = 193 (87 males, 106 females); mean age 50.4 (10.5) years; baseline sitting SBP 150.9 (11.3) mm Hg, DBP 99.9 (4.2) mm Hg; losartan 50 mg/HCTZ 0 mg: n = 59 (28 males, 31 females); mean age 47.2 (9.8) years; baseline sitting SBP 149.1 (10.6) mm Hg, DBP 100.2 (4.2) mm Hg; placebo: n = 188 (77 males, 111 females); mean age 50.6 (10.2) years; baseline sitting SBP 151.4 (12.1) mm Hg, DBP 99.8 (3.9) mm Hg<br><br>**Interventions:** Losartan 50 mg once daily; losartan 50 mg/HCTZ 0 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source**: Merck & Co.<br><br>**Notes:** Used week 4 BP data only, combined BP data for losartan monotherapy and losartan/HCTZ combination arms; BP change reported; SD of change not reported; endpoint BP and SD not reported; baseline SD |

| Study | Study Description |
|---|---|
| | reported; imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; DBP data from Figure 2, p. 1201, SBP data from Figure 3, p. 1202; WDAE reported at endpoint but not at week 4 |
| Flack 2003 [47] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 16 weeks total, titration-to-response every 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean DBP 95-109 mm Hg and mean SBP < 180 mm Hg<br><br>**Participants:** Losartan 50 mg: n = 188 (83 males, 105 females); mean age 52.0 (10.3) years; n = 184: baseline sitting SBP 150.7 (11.6) mm Hg, DBP 99.2 (3.5) mm Hg, HR 71.5 (8.8) bpm; placebo: n = 181 (84 males, 97 females); mean age 52.1 (11.1) years; n = 177: baseline sitting SBP 148.9 (11.6) mm Hg, DBP 99.1 (3.6) mm Hg, HR 73.1 (8.9) bpm<br><br>**Interventions:** Losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source**: Pharmacia<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change reported, endpoint BP and SD not reported, baseline SD reported; time of BP measurement not reported; BP data from Figure 1, p. 1152; WDAE reported at endpoint but not at week 4 |
| Fogari 2001 [31] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 12 weeks total, titration-to-response after 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Postmenopausal women (51-60 years old) with DBP 91-105 mm Hg and SBP < 180 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 29; mean age 55.1 (2.0) years; baseline SBP 159.8 (12.3) mm Hg, DBP 100.5 (7.2) mm Hg, HR 76.8 (8.9) bpm; irbesartan 150 mg: n = 28; mean age 55.2 (2.3) years; baseline SBP 160.6 (13.0) mm Hg, DBP 100.9 (5.9) mm Hg, HR 75.9 (8.8) bpm; losartan 50 mg: n = 28; mean age 54.7 (2.3) years; baseline SBP 160.2 (12.1) mm Hg, DBP 99.8 (7.1) mm Hg, HR 76.1 (8.6) bpm; valsartan 80 mg: n = 30; mean age 54.8 (2.2) years; baseline SBP 161.2 (11.9) mm Hg, DBP 101.3 (6.7) mm Hg, HR 77.2 (9.2) bpm; placebo: n = 25; mean age 55.1(2.1) years; baseline |

| Study | Study Description |
|---|---|
| | SBP 159.7 (11.5) mm Hg, DBP 100.6 (6.1) mm Hg, HR 75.7 (9.1) bpm<br><br>**Interventions:** Candesartan 8 mg once daily; irbesartan 150 mg once daily; losartan 50 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using standard mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** not reported<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change not reported, week 6 BP and SD reported, imputed 6-week SD for SD of change; BP data from Table II, p. 73 |
| Gradman 1995<br><br>[48] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 8 weeks total<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** mean supine DBP 100-115 mm Hg<br><br>**Participants:** Losartan 10 mg: n = 80 (51 males, 29 females); median age 55 years; baseline SBP 160.7 mm Hg, DBP 104.3 mm Hg; losartan 25 mg: n = 82 (55 males, 27 females); median age 53 years; baseline SBP 158.7 mm Hg, DBP 103.3 mm Hg; losartan 50 mg: n = 79 (53 males, 26 females); median age 53 years; baseline SBP 158.3 mm Hg, DBP 104.1 mm Hg; losartan 100 mg: n = 90 (59 males, 31 females); median age 52.5 years; baseline SBP 156.3 mm Hg, DBP 104.1 mm Hg; losartan 150 mg: n = 84 (62 males, 22 females); median age 56 years; baseline SBP 158.6 mm Hg, DBP 103.4 mm Hg; placebo: n = 78 (47 males, 31 females); median age 53 years; baseline SBP 157.9 mm Hg, DBP 103.3 mm Hg<br><br>**Interventions:** Losartan 10 mg once daily; losartan 25 mg once daily; losartan 50 mg once daily; losartan 100 mg once daily; losartan 150 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP; Mean change from baseline in peak supine SBP/DBP; WDAE<br><br>**Funding source: Merck & Co.**<br><br>**Notes:** BP change and SD of change reported, endpoint BP reported; endpoint SD not reported, BP data from Table 2, p.1348; BP measurement device not reported |

| Study | Study Description |
|---|---|
| Hedner 1999<br>[49] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks total, forced titration at week 4<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 551 (313 males, 238 females); mean age 55.7 (10.9) years; baseline sitting SBP 157.0 (16.3) mm Hg, DBP 101.4 (4.6) mm Hg, HR 73.9 (9.8) bpm; losartan 50 mg: n = 545 (309 males, 236 females); mean age 54.9 (10.5) years; baseline sitting SBP 157.4 (15.9) mm Hg, DBP 101.6 (5.1) mm Hg, HR 73.7 (9.0) bpm; placebo: n = 273 (157 males, 116 females); mean age 55.2 (10.5) years; baseline sitting SBP 157.8 (16.3) mm Hg, DBP 101.9 (5.2) mm Hg, HR 73.6 (9.7) bpm<br><br>**Interventions:** losartan 50 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported, baseline SD reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; BP data from text and Figure 1, p. 416 |
| Ikeda 1997<br>[50] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 12 weeks total, titrated to response at week 6<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Sitting DBP 95-115 mm Hg<br><br>**Participants:** Losartan 50 mg: n = 250 (161 males, 89 females); mean age 54.1 years; baseline DBP 102.2 mm Hg; placebo: n = 116 (74 males, 42 females); mean age 53.8 years; baseline DBP 101.3 mm Hg<br><br>**Interventions:** Losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br>**Funding source: Merck**<br>**Notes:** Used week 6 BP data only; BP change reported, DBP SD of change |

| Study | Study Description |
|---|---|
| | reported only, endpoint BP reported, endpoint DBP SD reported only, baseline SD not reported; imputed overall trial mean SBP SD of change; DBP data from Table 2 and SBP data from Figure 2, p. 38 |
| Kassler-Taub 1998 [42] | **Design:** Placebo run-in period: 4-5 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-110 mm Hg, with the two readings not differing by more than 8 mm Hg<br><br>**Participants:** Irbesartan 150 mg: n = 142 (77 males, 65 females); mean age 53.1 (10.5) years; baseline sitting SBP 155.3 (16.2) mm Hg, DBP 101.1 (4.6) mm Hg; irbesartan 300 mg: n = 140 (80 males, 60 females); mean age 55.6 (10.4) years; baseline sitting SBP 155.4 (16.0) mm Hg, DBP 100.4 (4.5) mm Hg; losartan 100 mg: n = 138 (69 males, 69 females); mean age 55.0 (10.7) years; baseline sitting SBP 153.3 (15.5) mm Hg, DBP 100.6 (4.4) mm Hg; placebo: n = 147 (90 males, 57 females); mean age 53.8 (9.6) years; baseline sitting SBP 152.4 (14.7) mm Hg, DBP 100.3 (4.3) mm Hg<br><br>**Interventions:** Irbesartan 150 mg once daily; irbesartan 300 mg once daily; losartan 100 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Bristol-Myers Squibb<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; baseline SD not reported, calculated SD from N and SE; BP data from Table 2, p. 448 |
| Mallion 1999 [51] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg and SBP 140-200 mm Hg<br><br>**Participants:** Telmisartan 40 mg: n = 57 (38 males, 19 females); mean age 58 years: baseline supine SBP 161.9 (14.7) mm Hg, DBP 100.8 (4.2) mm Hg, HR 70.8 (10.3) bpm; telmisartan 80 mg: n = 54 (35 males, 19 females); mean age 57 years; baseline supine SBP 164.2 (15.3) mm Hg, DBP 101.8 (4.9) mm Hg, HR 69.6 (8.5) bpm; losartan 50 mg: n = 57 (33 males, 24 females); mean age 56 years; baseline supine SBP 162.4 (16.3) mm Hg, DBP |

| Study | Study Description |
|---|---|
| | 100.7 (4.5) mm Hg, HR 70.6 (9.1) bpm; placebo: n = 55 (44 males, 11 females); mean age 54 years; baseline supine SBP 156.5 (14.7) mm Hg, DBP 99.2 (3.9) mm Hg, HR 67.9 (8.3) bpm<br><br>**Interventions:** Telmisartan 40 mg once daily; telmisartan 80 mg once daily; losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; calculated SD from SE and N; BP data from Table 3, p. 660 |
| Schoenberger 1995<br>[52] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg after 4 weeks with less than 7 mm Hg variation from sitting DBP reading at week 2<br><br>**Participants:** Losartan 50 mg: n = 139 (90 males, 49 females); median age 55 years; baseline sitting DBP 100.9 mm Hg; placebo: n = 140 (81 males, 59 females); median age 54 years; baseline sitting DBP 101.3 mm Hg<br><br>**Interventions:** Losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP; WDAE<br><br>**Funding source:** Merck<br><br>**Notes:** BP change and SD of change reported, endpoint BP reported; endpoint SD reported, BP data from Tables 2 and 3, p. S45; BP measurement device not reported |
| Weber 1995<br>[53]<br>Multiple publications:<br>Byyny 1996 [54]<br>Byyny 1995 [55]<br>Weber 1995b [56] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** All patients: n = 122 (83 males, 39 females); mean age 53 (11) years; baseline BP for all randomized patients not reported; losartan 50 mg once daily: n = 29; losartan 100 mg once daily: n = 30; losartan 50 mg twice daily: n = 31; placebo: n = 32 |

| Study | Study Description |
|---|---|
| | **Interventions:** Losartan 50 mg once daily; losartan 100 mg once daily; losartan 50 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Merck<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD reported; SBP data from Figure 2, p. S32, DBP data from Figure 3, p. S33 |
| White 2002<br>[57] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 8 weeks total, forced titration at week 4<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg during 2 consecutive weeks; also required that ambulatory awake DBP ≥ 85 mm Hg<br><br>**Participants:** Losartan 50 mg: n = 103 (64 males, 39 females); mean age 55 (10) years; baseline SBP 148 (14) mm Hg, DBP 95 (7) mm Hg, HR 72 (9) bpm; placebo: n = 46 (30 males, 16 females); mean age 56 (11) years; baseline SBP 148 (12) mm Hg, DBP 95(6) mm Hg, HR 71 (9) bpm<br><br>**Interventions:** Losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week BP data only; BP change and SD of change reported; BP data from Table IV, p. 663 |

**Table 3.6: Characteristics of included studies evaluating olmesartan**

| Study | Study Description |
|---|---|
| Chrysant 2003<br>[58] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg at both week 3 and week 4 visits, with a difference of 10 mm Hg or less between two visit means<br><br>**Participants:** Olmesartan 20 mg: n = 188 (116 males, 72 females); mean age |

| Study | Study Description |
|---|---|
| | 51.7 years; baseline sitting SBP 154.9 mm Hg, DBP 104.0 mm Hg; placebo: n = 66 (44 males, 22 females); mean age 52.0 years; baseline sitting SBP 154.2 mm Hg, DBP 103.3 mm Hg<br><br>**Interventions:** Olmesartan 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP; WDAE<br><br>**Funding source:** Sankyo Pharma<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported, baseline SD not reported; imputed overall trial mean SBP/DBP SD of change; BP data from Table 3, p. 429; BP measurement device not reported |
| Chrysant 2004 [59] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg at both week 3 and week 4 visits, with a difference of 7 mm Hg or less between two visit means<br><br>**Participants:** Olmesartan 10 mg: n = 39 (24 males, 15 females); mean age 49.9 (10.9) years; baseline sitting SBP 153.6 mm Hg, DBP 104.1 mm Hg; olmesartan 20 mg: n = 41 (21 males, 20 females); mean age 54.1 (9.9) years; baseline sitting SBP 154.6 mm Hg, DBP 103.2 mm Hg; olmesartan 40 mg: n = 45 (28 males, 17 females); mean age 54.4 (11.2) years; baseline sitting SBP 152.9 mm Hg, DBP 102.6 mm Hg; placebo: n = 42 (27 males, 15 females); mean age 54.0 (9.9) years; baseline sitting SBP 152.1 mm Hg, DBP 103.4 mm Hg<br><br>**Interventions:** Olmesartan 10 mg once daily; olmesartan 20 mg once daily; olmesartan 40 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP<br><br>**Funding source:** Sankyo Pharma<br><br>**Notes:** BP and SD of change not reported, endpoint BP reported, endpoint SD not reported, baseline SD not reported; imputed overall trial mean SBP/DBP SD of change; BP data from Table 2, p. 256; BP measurement device not reported |
| Neutel 2002 | **Design:** Placebo run-in period: 2-3 weeks; Treatment duration: 8 weeks |

| Study | Study Description |
|---|---|
| [60] | **Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 100-115 mm Hg<br><br>**Participants:** Olmesartan 5 mg once daily: n = 45 (30 males, 15 females); mean age 56 years; baseline sitting SBP 151 mm Hg, DBP 96 mm Hg; olmesartan 20 mg once daily: n = 45 (31 males, 14 females); mean age 52 years; baseline 24h SBP 149 mm Hg, DBP 96 mm Hg; olmesartan 80 mg once daily: n = 48 (32 males, 16 females); mean age 52 years; baseline 24h SBP 148 mm Hg, DBP 95 mm Hg; olmesartan 2.5 mg twice daily: n = 50 (34 males, 16 females); mean age 53 years; baseline 24h SBP 148 mm Hg, DBP 94 mm Hg; olmesartan 10 mg twice daily: n = 48 (29 males, 19 females); mean age 53 years; baseline 24h SBP 148 mm Hg, DBP 95 mm Hg; olmesartan 40 mg twice daily: n = 50 (34 males, 16 females); mean age 56 years; baseline 24h SBP 151 mm Hg, DBP 95 mm Hg; placebo: n = 48 (29 males, 19 females); mean age 53 years; baseline 24 h SBP 149 mm Hg, DBP 94 mm Hg<br><br>**Interventions:** Olmesartan 5 mg once daily; olmesartan 20 mg once daily; olmesartan 80 mg once daily; olmesartan 2.5 mg twice daily; olmesartan 10 mg twice daily; olmesartan 40 mg twice daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP; WDAE<br><br>**Funding source:** Sankyo Pharma<br><br>**Notes:** SBP change reported for olmesartan groups, SBP change not reported for placebo group, SBP SD of change not reported for all groups, DBP change reported for all groups, DBP SD of change not reported for all groups, endpoint BP and SD not reported, baseline SD not reported; imputed overall trial mean SBP/DBP SD of change; BP data from Figure 3, p. 327; BP measurement device not reported |

**Table 3.7: Characteristics of included studies evaluating tasosartan**

| Study | Study Description |
|---|---|
| Feldman 1997<br>[61] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 9 weeks total, titration-to-response at 3 and 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3 |

| Study | Study Description |
|---|---|
| | **Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Tasosartan 25 mg: n = 71 (51 males, 20 females); mean age 53.5 (8.8) years; baseline sitting SBP 154.1 mm Hg, DBP 101.2 mm Hg; placebo: n = 71 (55 males, 16 females); mean age 50.9 (10.5) years; baseline sitting SBP 151.5 mm Hg, DBP 101.6 mm Hg<br><br>**Interventions:** Tasosartan 25 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP<br><br>**Funding source:** Not reported<br><br>**Notes:** Used week 3 BP data only; BP change reported; SD of change not reported; endpoint BP and SD not reported; baseline SBP/DBP SD not reported; imputed overall trial mean SD of change for SBP and DBP; BP data from Table 2, p. 296; WDAE reported at endpoint but not at week 3; BP measurement device not reported |
| Lacourciere 1998 [62] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg<br><br>**Participants:** Tasosartan 10 mg: n = 57 (40 males, 17 females); mean age 54 years: baseline sitting SBP 152 mm Hg, DBP 101 mm Hg; tasosartan 30 mg: n = 55 (43 males, 12 females); mean age 52 years; baseline sitting SBP 151 mm Hg, DBP 101 mm Hg; tasosartan 100 mg: n = 55 (36 males, 19 females); mean age 53 years; baseline sitting SBP 152 mm Hg, DBP 101 mm Hg; tasosartan 300 mg: n = 55 (35 males, 20 females); mean age 53 years; baseline sitting SBP 152 mm Hg, DBP 101 mm Hg; placebo: n = 56 (33 males, 23 females); mean age 55 years; baseline sitting SBP 152 mm Hg, DBP 100 mm Hg<br><br>**Interventions:** Tasosartan 10 mg once daily; tasosartan 30 mg once daily; tasosartan 100 mg once daily; tasosartan 300 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Wyeth Ayerst Research<br><br>**Notes:** BP change and 95% CI of change reported for tasosartan groups, BP |

| Study | Study Description |
|---|---|
| | change reported for placebo group, 95% CI of BP change not reported for placebo group, endpoint BP and SD not reported; calculated SD of change from 95% CI of change for tasosartan groups; imputed overall trial mean SBP/DBP SD of change for placebo group; BP data from Figure 1, p. 457; 95% CI data from text, p. 457 |
| Neutel 1999<br>[63] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 10 weeks total, titration-to-response at 3 and 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg and did not vary by more than 10 mm Hg for each of three visits<br><br>**Participants:** Tasosartan 50 mg: n = 132 (88 males, 44 females); mean age 52.2 (9.6) years; baseline sitting SBP 150.6 (13.8) mm Hg, DBP 100.3 (8.0) mm Hg; placebo: n = 130 (92 males, 38 females); mean age 52.5 (9.7) years; baseline sitting SBP 150.1 (13.7) mm Hg, DBP 100.3 (8.0) mm Hg<br><br>**Interventions:** Tasosartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Wyeth Ayerst Research<br><br>**Notes:** Used week 3 BP data only; BP and SD of change reported, endpoint BP and SD not reported; DBP data from Figure 1, p. 120; SBP data from Figure 2, p. 120 |

**Table 3.8: Characteristics of included studies evaluating telmisartan**

| Study | Study Description |
|---|---|
| Mallion 1999<br>[51] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg and SBP 140-200 mm Hg<br><br>**Participants:** Telmisartan 40 mg: n = 57 (38 males, 19 females); mean age 58 years: baseline supine SBP 161.9 (14.7) mm Hg, DBP 100.8 (4.2) mm Hg, HR 70.8 (10.3) bpm; telmisartan 80 mg: n = 54 (35 males, 19 females); mean age 57 years; baseline supine SBP 164.2 (15.3) mm Hg, DBP 101.8 |

| Study | Study Description |
|---|---|
| | (4.9) mm Hg, HR 69.6 (8.5) bpm; losartan 50 mg: n = 57 (33 males, 24 females); mean age 56 years; baseline supine SBP 162.4 (16.3) mm Hg, DBP 100.7 (4.5) mm Hg, HR 70.6 (9.1) bpm; placebo: n = 55 (44 males, 11 females); mean age 54 years; baseline supine SBP 156.5 (14.7) mm Hg, DBP 99.2 (3.9) mm Hg, HR 67.9 (8.3) bpm<br><br>**Interventions:** Telmisartan 40 mg once daily; telmisartan 80 mg once daily; losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br>**Funding source:** Not reported<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported; calculated SD from SE and N; BP data from Table 3, p. 660 |
| Manolis 2004<br>[64] | **Design:** Placebo run-in period: 2-4 weeks; Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting SBP/DBP of 150-179/<90 mm Hg<br><br>**Participants:** Telmisartan 20 mg: n = 206 (87 males, 119 females); mean age 63.0 (11.5) years: baseline sitting SBP 163.5 (8.0) mm Hg, DBP 83.7 (5.2) mm Hg, HR 72.4 (10.0) bpm; telmisartan 40 mg: n = 210 (87 males, 123 females); mean age 62.7 (10.8) years: baseline sitting SBP 162.7 (8.2) mm Hg, DBP 83.4 (4.6) mm Hg, HR 72.1 (9.9) bpm; telmisartan 80 mg: n = 207 (91 males, 116 females); mean age 62.5 (10.9) years; baseline sitting SBP 162.4 (8.2) mm Hg, DBP 83.2 (5.1) mm Hg, HR 72.4 (9.9) bpm; placebo: n = 211 (90 males, 121 females); mean age 63.6 (10.2) years; baseline sitting SBP 163.3 (7.8) mm Hg, DBP 83.5 (5.1) mm Hg, HR 72.2 (9.9) bpm<br><br>**Interventions:** Telmisartan 20 mg once daily; telmisartan 40 mg once daily; telmisartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Boehringer Ingelheim<br><br>**Notes:** Used SBP data only; BP change reported, SD of change not reported, endpoint BP and SD not reported, baseline SD reported; imputed overall trial mean SBP SD of change since SBP levels used as inclusion criteria; BP data |

| Study | Study Description |
|---|---|
| | from text, p. 1035 |
| McGill 2001<br>[65]<br>Duplicate publication: McGill 2001 [66] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = A; Jadad score = 5<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg during last 2 weeks of run-in, which could not vary by > 7mm Hg from visit to visit or by > 10mm Hg over this 2-week period, and mean supine SBP 140-200 mm Hg at randomization<br><br>**Participants:** Telmisartan 20-160 mg: n = 209 (117 males, 92 females); mean age 51 years; ITT: n = 208; baseline supine SBP 153.2 (12.0) mm Hg, DBP 100.7 (4.6) mm Hg, HR 71.2 (9.2) bpm; placebo: n = 74 (45 males, 29 females); mean age 55 years; ITT: n = 73; baseline supine SBP 153.7 (11.3) mm Hg, DBP 100.3 (3.9) mm Hg, HR 71.9 (9.3) bpm<br><br>**Interventions:** Telmisartan 20 mg once daily; telmisartan 40 mg once daily; telmisartan 80 mg once daily; telmisartan 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Boehringer Ingelheim<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table IV, p. 841 and Figure 2, p. 843 |
| Neutel 1998<br>[67] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 100-114 mm Hg<br><br>**Participants:** Telmisartan 20 mg: n = 47 (32 males, 15 females); mean age 52 (9.6) years; baseline supine SBP 153.0 mm Hg, DBP 103.0 mm Hg; telmisartan 40 mg: n = 47 (32 males, 15 females); mean age 54.3 (7.1) years; baseline supine SBP 148.8 mm Hg, DBP 101.5 mm Hg; telmisartan 80 mg: n = 44 (32 males, 12 females); mean age 51.4 (9.7) years; baseline supine SBP 153.1 mm Hg, DBP 103.1 mm Hg; telmisartan 120 mg: n = 45 (31 males, 14 females); mean age 50.8 (10.2) years; baseline supine SBP 149.8 mm Hg, DBP 102.1 mm Hg; telmisartan 160 mg: n = 45 (33 males, 12 females); mean age 53 (9.7) years; baseline supine SBP 152.7 mm Hg, DBP 101.9 mm Hg; placebo: n = 46 (29 males, 17 females); mean age 52 (8.2) years; |

| Study | Study Description |
|---|---|
| | baseline supine SBP 152.9 mm Hg, DBP 102.5 mm Hg<br><br>**Interventions:** Telmisartan 20 mg once daily; telmisartan 40 mg once daily; telmisartan 80 mg once daily; telmisartan 120 mg once daily; telmisartan 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; adjusted mean change from baseline in HR; WDAE<br><br>**Funding source:** Not reported<br><br>**Notes:** BP change and SE of change reported, endpoint BP and SD not reported, baseline SD reported; calculated SD from N and SE; BP data from Table 2, p. 211 |
| Smith 1998<br>[68] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean supine DBP 95-114 mm Hg<br><br>**Participants:** Telmisartan 40 mg: n = 72 (50 males, 22 females); mean age 54.6 (12.0) years; baseline supine SBP 155.2 (14.3) mm Hg, DBP 100.8 (4.3) mm Hg; telmisartan 80 mg: n = 72 (41 males, 31 females); mean age 54.4 (10.4) years; baseline supine SBP 153.7 (13.0) mm Hg, DBP 100.0 (3.6) mm Hg; telmisartan 120 mg: n = 73 (48 males, 25 females); mean age 53.2 (11.0) years; baseline supine SBP 151.9 (10.4) mm Hg, DBP 100.2 (4.0) mm Hg; telmisartan 160 mg: n = 75 (51 males, 24 females); mean age 53.4 (10.5) years; baseline supine SBP 154.2 (14.6) mm Hg, DBP 100.5 (4.9) mm Hg; placebo: n = 76 (49 males, 27 females); mean age 55.6 (9.6) years; baseline supine SBP 154.8 (11.8) mm Hg, DBP 100.4 (4.5) mm Hg<br><br>**Interventions:** Telmisartan 40 mg once daily; telmisartan 80 mg once daily; telmisartan 120 mg once daily; telmisartan 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Boehringer Ingelheim Pharma<br><br>**Notes:** BP change and SE of change reported; endpoint BP and SD not reported; calculated SD of change from N and SE of change; change in BP data from Figures 1 and 2, p. 235; SE of change data from Table 2, p. 234 |

| Study | Study Description |
|---|---|
| Smith 2000<br><br>[69] | **Design:** Placebo run-in period: 4 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 100-114 mm Hg during final 2 weeks of run-in, mean supine DBP could not vary by more than 7 mm Hg between weeks 2 and 3 or weeks 3 and 4 of run-in, or by more than 10 mm Hg between weeks 2 and 4 of run-in<br><br>**Participants:** Telmisartan 40 mg: n = 40 (23 males, 17 females); mean age 54.3 years; baseline supine SBP 154.6 mm Hg, DBP 102.4 mm Hg, HR 71.8 bpm; telmisartan 80 mg: n = 41 (26 males, 15 females); mean age 50.6 years; baseline supine SBP 154.2 mm Hg, DBP 103.1 mm Hg, HR 72.0 bpm; telmisartan 120 mg: n = 41 (25 males, 16 females); mean age 52.0 years; baseline supine SBP 153.9 mm Hg, DBP 102.0 mm Hg, HR 72.0 bpm; placebo: n = 43 (24 males, 19 females); mean age 52.0 years; baseline supine SBP 159.5 mm Hg, DBP 104.9 mm Hg, HR 72.5 bpm<br><br>**Interventions:** Telmisartan 40 mg once daily; telmisartan 80 mg once daily; telmisartan 120 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough standing SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer; mean change from baseline in trough standing HR; mean change from baseline in trough supine HR; WDAE<br><br>**Funding source:** Boehringer Ingelheim Pharma<br><br>**Notes:** BP change and SE of change reported; endpoint BP and SD not reported; calculated SD of change from N and SE of change; change in BP data from Table II, p. 1385 |

**Table 3.9: Characteristics of included studies evaluating valsartan**

| Study | Study Description |
|---|---|
| Benz 1998<br><br>[70] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg and a difference between enrolment and randomisation not > 10 mm Hg |

| Study | Study Description |
|---|---|
| | **Participants:** Valsartan 80 mg: n = 99 (63 males, 36 females); mean age 52 (10.2) years: baseline sitting SBP 153.7 (14.4) mm Hg, DBP 101.5 (4.9) mm Hg; valsartan 160 mg: n = 99 (61 males, 38 females); mean age 52 (10.5) years: baseline sitting SBP 153.5 (15.1) mm Hg, DBP 101.5 (4.8) mm Hg; placebo: n = 94 (58 males, 36 females); mean age 52 (10.4) years: baseline sitting SBP 152.7 (17.1) mm Hg, DBP 101.4 (5.0) mm Hg<br><br>**Interventions:** Valsartan 80 mg once daily; valsartan 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Placebo-corrected BP change reported, SD of change not reported, endpoint BP and SD not reported, baseline SD reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; BP data from Table 2, p. 864 |
| Black 1997<br>[71] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 12 weeks total, titration-to-response at 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg and SBP < 180 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 364 (144 males, 220 females); mean age 53.5 (11.1) years; baseline sitting SBP 153.9 (14.9) mm Hg, DBP 101.0 (4.5) mm Hg; placebo: n = 183 (113 males, 70 females); mean age 54.0 (11.8) years; baseline sitting SBP 154.0 (15.0) mm Hg, DBP 101.3 (4.6) mm Hg<br><br>**Interventions:** Valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Least mean square change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** Used week 4 BP data only; BP change reported, SD of change not reported, endpoint BP and SD not reported; imputed SBP SD of change from baseline SBP SD of change, imputed overall trial mean DBP SD of change; SBP data from Figure 1, p. 487, DBP data from text, p. 485 |

| Study | Study Description |
|---|---|
| Fogari 2001<br>[31] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 12 weeks total, titration-to-response after 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Postmenopausal women (51-60 years old) with DBP 91-105 mm Hg and SBP < 180 mm Hg<br><br>**Participants:** Candesartan 8 mg: n = 29; mean age 55.1 (2.0) years; baseline SBP 159.8 (12.3) mm Hg, DBP 100.5 (7.2) mm Hg, HR 76.8 (8.9) bpm; irbesartan 150 mg: n = 28; mean age 55.2 (2.3) years; baseline SBP 160.6 (13.0) mm Hg, DBP 100.9 (5.9) mm Hg, HR 75.9 (8.8) bpm; losartan 50 mg: n = 28; mean age 54.7 (2.3) years; baseline SBP 160.2 (12.1) mm Hg, DBP 99.8 (7.1) mm Hg, HR 76.1 (8.6) bpm; valsartan 80 mg: n = 30; mean age 54.8 (2.2) years; baseline SBP 161.2 (11.9) mm Hg, DBP 101.3 (6.7) mm Hg, HR 77.2 (9.2) bpm; placebo: n = 25; mean age 55.1(2.1) years; baseline SBP 159.7 (11.5) mm Hg, DBP 100.6 (6.1) mm Hg, HR 75.7 (9.1) bpm<br><br>**Interventions:** Candesartan 8 mg once daily; irbesartan 150 mg once daily; losartan 50 mg once daily; valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using standard mercury sphygmomanometer; trough sitting HR<br><br>**Funding source:** not reported<br><br>**Notes:** Used week 6 BP data only; BP change and SD of change not reported, week 6 BP and SD reported, imputed 6-week SD for SD of change; BP data from Table II, p. 73 |
| Hanefeld 2001<br>[72] | **Design:** Placebo run-in period: 3 weeks. Treatment duration: 12 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting DBP 91-105 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 63 (28 males, 35 females); mean age 57.4 (10.8) years; baseline sitting SBP 163.9 (12.5) mm Hg, DBP 97.2 (5.2) mm Hg, HR 72.2 (6.1) bpm; placebo: n = 60 (33 males, 27 females); mean age 58.8 (11.1) years; baseline sitting SBP 167.0 (14.1) mm Hg, DBP 98.5 (3.4) mm Hg, HR 73.6 (7.9) bpm<br><br>**Interventions:** Valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough |

| Study | Study Description |
|---|---|
| | sitting SBP/DBP; mean change from baseline in trough sitting HR<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; baseline SD reported; BP data from Table 3, p. 275; BP measurement device not reported |
| Hedner 1999<br>[49] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks total, forced titration at week 4<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 551 (313 males, 238 females); mean age 55.7 (10.9) years; baseline sitting SBP 157.0 (16.3) mm Hg, DBP 101.4 (4.6) mm Hg, HR 73.9 (9.8) bpm; losartan 50 mg: n = 545 (309 males, 236 females); mean age 54.9 (10.5) years; baseline sitting SBP 157.4 (15.9) mm Hg, DBP 101.6 (5.1) mm Hg, HR 73.7 (9.0) bpm; placebo: n = 273 (157 males, 116 females); mean age 55.2 (10.5) years; baseline sitting SBP 157.8 (16.3) mm Hg, DBP 101.9 (5.2) mm Hg, HR 73.6 (9.7) bpm<br><br>**Interventions:** Valsartan 80 mg once daily; losartan 50 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** Used week 4 BP data only; BP change and SD of change not reported, endpoint BP reported, endpoint SD not reported, baseline SD reported; imputed baseline SBP SD for SBP SD of change; imputed overall trial mean DBP SD of change; BP data from text and Figure 1, p. 416 |
| Holwerda 1996<br>[73] | **Design:** Placebo run-in period: 2 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-115 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 137 (65 males, 72 females); mean age 53.1 (12.4) years; baseline sitting SBP 161.7 (11.6) mm Hg, DBP 101.2 (4.5) mm Hg; enalapril 20 mg: n = 69 (40 males, 29 females); mean age 52.5 (10.3) years; baseline sitting SBP 161.5 (10.4) mm Hg, DBP 102.2 (4.2) mm |

| Study | Study Description |
|---|---|
| | Hg; placebo: n = 142 (76 males, 66 females); mean age 53.1 (12.9) years; baseline sitting SBP 161.0 (11.5) mm Hg, DBP 101.8 (4.4) mm Hg<br><br>**Interventions:** Valsartan 80 mg once daily; enalapril 20 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Trough sitting SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change and SD of change not reported, endpoint BP and SD reported; imputed endpoint SD for SD of change; BP data from Table 3, p. 1150 |
| Klingbeil 2002 [74]<br>Duplicate publication: Klingbeil 2003 [75] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 6 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 2<br><br>**Inclusion criteria:** Mean sitting BP ≥ 160/95 mm Hg and < 220/115 mm Hg<br><br>**Participants:** Valsartan 80 mg: n = 20 (13 males, 7 females); mean age 52 (9) years; baseline sitting SBP 171 (9) mm Hg, DBP 102 (3) mm Hg, HR 70.6 (8.3) bpm; placebo: n = 20 (8 males, 12 females); mean age 52 (9) years; baseline sitting SBP 174 (8) mm Hg, DBP 102 (3) mm Hg, HR 70.3 (6.8) bpm<br><br>**Interventions:** Valsartan 80 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP<br><br>**Funding source:** Novartis Pharma<br><br>**Notes:** BP change and SD of change reported, endpoint BP and SD not reported; BP data from text, p. 2425; BP measurement device not reported |
| Oparil 1996 [76] | **Design:** Placebo run-in period: 2-4 weeks. Treatment duration: 8 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean sitting BP 95-115 mm Hg<br><br>**Participants:** Valsartan 20 mg: n = 140 (93 males, 47 females); mean age 53.8 years; baseline sitting SBP 151.6 mm Hg, DBP 100.8 mm Hg; valsartan 80 mg: n = 150 (88 males, 62 females); mean age 53.6 years; baseline sitting SBP 152.1 mm Hg, DBP 100.9 mm Hg; valsartan 160 mg: n = 148 (94 |

| Study | Study Description |
|---|---|
| | males, 54 females); mean age 52.0 years; baseline sitting SBP 149.9 mm Hg, DBP 101.4 mm Hg; valsartan 320 mg: n = 150 (95 males, 55 females); mean age 53.7 years; baseline sitting SBP 151.0 mm Hg, DBP 101.3 mm Hg; placebo: n = 148 (98 males, 50 females); mean age 53.6 years; baseline sitting SBP 152.4 mm Hg, DBP 100.8 mm Hg<br><br>**Interventions:** Valsartan 20 mg once daily; valsartan 80 mg once daily; valsartan 160 mg once daily; valsartan 320 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Least squares mean change from baseline in trough sitting SBP/DBP using mercury sphygmomanometer; WDAE<br><br>**Funding source:** Ciba-Geigy Inc.<br><br>**Notes:** BP change reported, SD of change not reported, endpoint BP and SD not reported, baseline SD not reported; imputed overall trial mean SBP/DBP SD of change; BP data from text, p. 801 |
| Pool 1999<br>[77] | **Design:** Placebo run-in period: 4 weeks. Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 4<br><br>**Inclusion criteria:** Mean supine DBP 95-115 mm Hg<br><br>**Participants:** Valsartan 10 mg: n = 25 (19 males, 6 females); mean age 54.3 (10.1) years: baseline supine SBP 157.3 (13.8) mm Hg, DBP 102.6 (5.8) mm Hg; valsartan 40 mg: n = 25 (17 males, 8 females); mean age 52.4 (9.3) years; baseline supine SBP 150.7 (13.5) mm Hg, DBP 101.8 (5.3) mm Hg; valsartan 80 mg: n = 23 (19 males, 4 females); mean age 52.3 (12.9) years; baseline supine SBP 152.7 (13.4) mm Hg, DBP 100.7 (5.0) mm Hg; valsartan 160 mg: n = 24 (12 males, 12 females); mean age 52.2 (10.2) years; baseline supine SBP 155.1 (15.7) mm Hg, DBP 101.0 (5.2) mm Hg; placebo: n = 25 (12 males, 13 females); mean age 53.0 (9.3) years; baseline supine SBP 156.4 (17.6) mm Hg, DBP 101.7 (4.9) mm Hg<br><br>**Interventions:** Valsartan 10 mg once daily; valsartan 40 mg once daily; valsartan 80 mg once daily; valsartan 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Adjusted mean change from baseline in trough supine SBP/DBP using mercury sphygmomanometer<br><br>**Funding source:** Novartis Pharma |

| Study | Study Description |
|---|---|
| | **Notes:** BP change and SD of change not reported, endpoint BP and SD not reported, baseline SD reported; imputed baseline SBP SD for SBP SD of change, imputed overall trial mean DBP SD of change; BP data from text, p. 277 and p. 279 |

**Table 3.10: Characteristics of included studies evaluating KT3-671**

| Study | Study Description |
|---|---|
| Patterson 2003 [78] | **Design:** Placebo run-in period: 2 weeks; Treatment duration: 4 weeks<br><br>**Quality:** Cochrane method = B; Jadad score = 3<br><br>**Inclusion criteria:** Mean sitting DBP 95-114 mm Hg and mean sitting SBP ≤ 190 mm Hg<br><br>**Participants:** KT3-671 40 mg: ITT n = 65 (39 males, 26 females); mean age 55 years; baseline BP for ITT not reported; Per protocol n = 50; baseline sitting SBP = 162.1 (13.6) mm Hg, DBP = 102.4 (4.8) mm Hg; KT3-671 80 mg: ITT n = 58 (42 males, 16 females); mean age 53 years; baseline BP for ITT not reported; Per protocol n = 51; baseline sitting SBP not reported, DBP 101.5 (4.7) mm Hg; KT3-671 160 mg: ITT n = 60 (42 males, 18 females); mean age 52 years; baseline BP for ITT not reported; Per protocol n = 48; baseline sitting SBP not reported, DBP 102.2 (4.8) mm Hg; placebo: ITT n = 61 (35 males, 26 females); mean age 54 years; baseline BP for ITT not reported; Per protocol n = 48; baseline sitting SBP 158.2 (11.8) mm Hg, DBP 101.4 (4.3) mm Hg<br><br>**Interventions:** KT3-671 40 mg once daily; KT3-671 80 mg once daily; KT3-671 160 mg once daily; placebo<br><br>**Primary and secondary outcomes:** Mean change from baseline in trough sitting SBP/DBP using automatic BP measuring device (Omron HEM 705CP); WDAE<br><br>**Funding source:** Kotobuki Pharma<br><br>**Notes:** BP and SD of change reported (for per protocol population only), endpoint BP and SD not reported; BP data from Table 2, p. 516 |

Baseline characteristics of the 46 included studies are provided in Table 3.11. A total of 13 451 participants with a mean age of 55.0 years and baseline blood pressure of

155.6/101.0 mm Hg were treated for a mean duration of 7.5 weeks. In most cases, the number of patients treated with an ARB was larger than the number of placebo-treated patients because many of the included studies have multiple treatment arms comparing different doses of an ARB and, in some trials, comparing different ARBs with a single placebo arm.

**Table 3.11: Overview of the 46 included studies evaluating ARBs as monotherapy**

| Drug<br>Daily dose range<br>Total studies | Number of ARB patients | Number of placebo patients | Mean age of patients | Mean baseline BP<br>Pulse pressure (mm Hg) | Mean duration of treatment (weeks) |
|---|---|---|---|---|---|
| candesartan<br>2 - 32 mg<br>5 studies | 762 | 280 | 55.1 | 158.4/101.7<br>56.7 | 7.3 |
| eprosartan<br>600 - 1200 mg<br>3 studies | 393 | 295 | 60.5 | 158.4/100.6<br>57.8 | 6.0 |
| irbesartan<br>37.5 - 300 mg<br>9 studies | 1239 | 652 | 54.5 | 152.5/100.6<br>51.9 | 8.5 |
| losartan<br>10 - 150 mg<br>12 studies | 2134 | 1287 | 54.9 | 156.5/101.1<br>55.4 | 7.4 |
| olmesartan<br>5 - 80 mg<br>3 studies | 446 | 155 | 52.6 | 152.6/101.0<br>51.6 | 8.0 |
| tasosartan<br>10 - 50 mg<br>3 studies | 315 | 257 | 52.8 | 151.5/100.7<br>50.8 | 7.4 |
| telmisartan<br>20 - 160 mg<br>6 studies | 1578 | 502 | 57.1 | 157.9/101.3<br>56.6 | 6.9 |
| valsartan<br>10 - 320 mg<br>9 studies | 2012 | 947 | 54.0 | 155.7/101.2<br>54.5 | 7.3 |
| KT3-671<br>40-160 mg<br>1 study | 149 | 48 | 53.5 | 160.2/101.9<br>58.3 | 4.0 |
| **TOTAL:**<br>46 studies<br>13 451 patients | 9028 | 4423 | 55.0 | 155.6/101.0<br>54.6 | 7.5 |

Table 3.11 demonstrates that there is sufficient RCT evidence for the various ARBs to generate dose-response curves for systolic and diastolic blood pressure reduction as well as accomplish the secondary goals of this review. These studies investigate most ARBs over a dose range that is wider than what is recommended by the manufacturers.

### 3.2.2 Imputation of missing variance data

Thirty (65%) of the included studies reported the standard deviation of the change in blood pressure. These values were used to calculate weighted mean estimates of the standard deviation of the change in SBP and DBP for the ARB and placebo groups. One trial reported SD of BP change values that were not within 3 standard deviations of the calculated weighted mean estimate [30]. This trial's outlier SD value was excluded from the calculation and the weighted mean estimate was adjusted accordingly. The weighted mean standard deviations of the change in SBP and DBP are 13.20 (SD 2.1) mm Hg and 7.8 (SD 1.7) mm Hg for the ARB group, respectively. For the placebo group, the standard deviation of the change was 12.40 (SD 3.8) mm Hg for SBP and 7.6 (SD 2.3) mm Hg for DBP. There was no statistically significant difference between the ARB and placebo groups for SD of SBP change or SD of DBP change. These values were used according to the imputation hierarchy for trials that did not report SD of BP change.

Sixteen (35%) of the included studies had SD of BP change value imputed. Of these studies, 1 trial was imputed using endpoint SD, 5 (11%) were imputed using baseline SD for SBP, 14 (30%) were imputed using the weighted mean SD of SBP change from other trials, and 12 (26%), were imputed using the weighted mean SD of DBP change from other trials.

### 3.2.3 Methodological quality of included studies

The Jadad and Cochrane scales were used in this review to assess the quality of the included studies. Forty four (95.7%) of the included trials did not report allocation concealment, while the remaining two (4.3%) trials reported an adequate method of concealment. The Jadad score for each included study is provided in the 'Notes' section of Tables 3.2 - 3.10. Using the Jadad quality score, 39 (84.8%) of the included studies were of good quality, 2 (5.1%) were of excellent quality, and 5 (10.9%) studies were of poor quality. Removing the studies that were considered poor according to the Jadad method did not alter the results of the meta-analysis. Rather, the Jadad score was not very useful for assessing the quality of trials included in this review because its scoring criteria were similar to two of the criteria for inclusion of studies in our systematic review; the studies had to be randomized and double-blind. Thus all included studies would score at least 2

on the Jadad scale. Furthermore, it was clear to us that the Jadad and Cochrane quality assessment scales were not evaluating the methodological quality of the trials but instead the quality of reporting in the published studies.

The accuracy of blood pressure measurement is the most crucial factor in the included studies, but this is not considered in the Jadad and Cochrane quality assessment scales. The quality of reporting of the blood pressure results in the included trials appeared to be independent of the quality of reporting of the methodology.

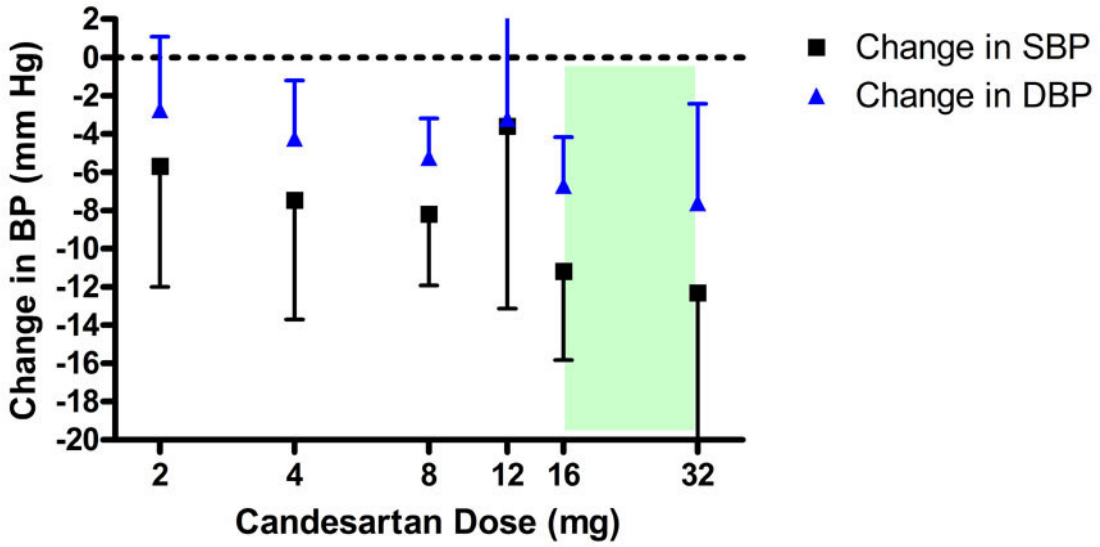
### 3.2.4 Dose-ranging BP lowering efficacy of individual ARB drugs

Summarized below are the dose-related trough blood pressure lowering efficacy estimates of each of the 9 ARBs that were administered once daily in the included studies. The weighted mean placebo effect across all trials was -2.3 (95% CI -2.8, -1.8; range -13.4 to 3.2) mm Hg and -3.3 (95% CI -3.6 - 3.0; range -7.7 to -0.4) mm Hg for SBP and DBP, respectively. Therefore, to determine the magnitude of the blood pressure lowering efficacy of each ARB, a weighted mean difference from placebo (ARB effect size minus placebo effect size) with a 95% confidence interval (in parentheses) was calculated.

#### 3.2.4.1 Dose-ranging BP lowering efficacy of candesartan

Five of the included trials assessed the blood pressure lowering efficacy of candesartan over the dose range of 2 to 32 mg/day (Figure 3.4).

**Figure 3.4: Log dose-response curve of candesartan 2 - 32 mg/day (Shaded area represents manufacturer's recommended dose range)**




Four trials reported the funding source and all were sponsored by the manufacturer of candesartan. Candesartan 2 mg/day did not show a statistically significant difference from placebo. Compared with placebo, the 12 mg/day dose also did not significantly reduce blood pressure but only one trial contributed to this efficacy estimate. However, doses immediately below and above 12 mg/day had sufficient trial evidence and they were significantly different than placebo.

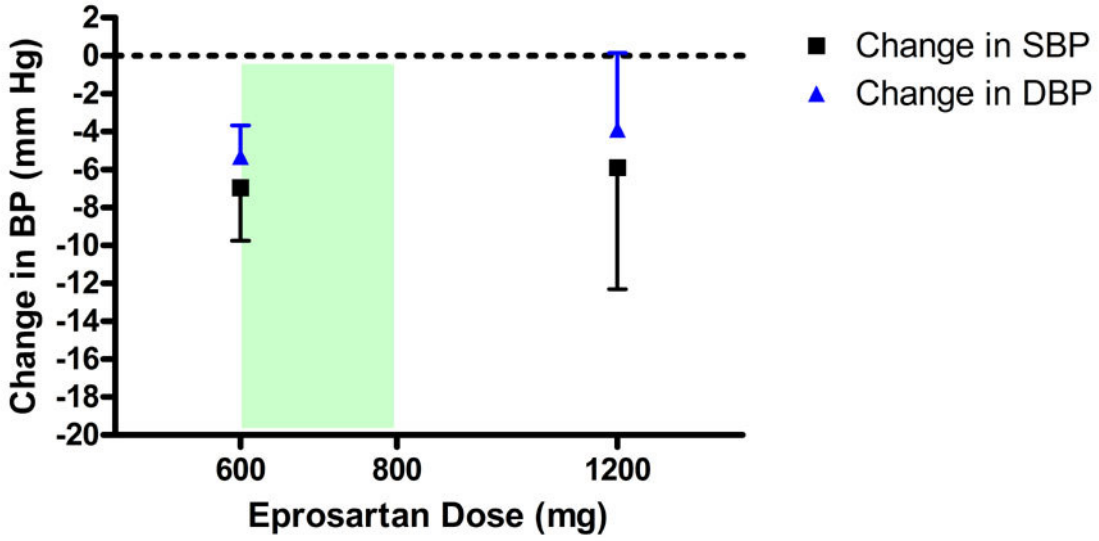
One trial in the 8 mg/day group had an exaggerated effect size of -14.30/-9.50 mm Hg [30]. This trial reported an extremely small standard deviation of the blood pressure change value in the placebo group but not for the candesartan group – a pattern that is inconsistent with all other trials included in this systematic review. A possible explanation for this is that blinding was compromised in the trial. The results of this suspicious trial were therefore excluded from the effect estimate.

The lowest effective dose was 4 mg/day, less than the manufacturer's recommended starting dose, and there was no statistically significant difference in effect sizes between doses in the 4 to 32 mg/day range using indirect comparisons. The best estimate of the near maximal blood pressure lowering efficacy of candesartan 4 to 32 mg/day is -8.93 (95% CI -11.37, -6.50) mm Hg for SBP and -5.59 (95% CI -6.95, -4.22) mm Hg for DBP.

### 3.2.4.2 Dose-ranging BP lowering efficacy of eprosartan

The manufacturer sponsored all four included trials that evaluated eprosartan (Figure 3.5). Nearly all the trial evidence assessed the recommended starting dose of 600 mg/day and no trials investigated the blood pressure lowering efficacy of the maximum recommended dose (800 mg/day). Only one trial reported efficacy data for 1200 mg/day, which did not demonstrate a statistically significant reduction in blood pressure compared with placebo. However, this is likely due to the wide confidence intervals associated with the effect size estimate.

**Figure 3.5: Log dose-response curve of eprosartan 600 - 1200 mg/day (Shaded area represents manufacturer's recommended dose range)**

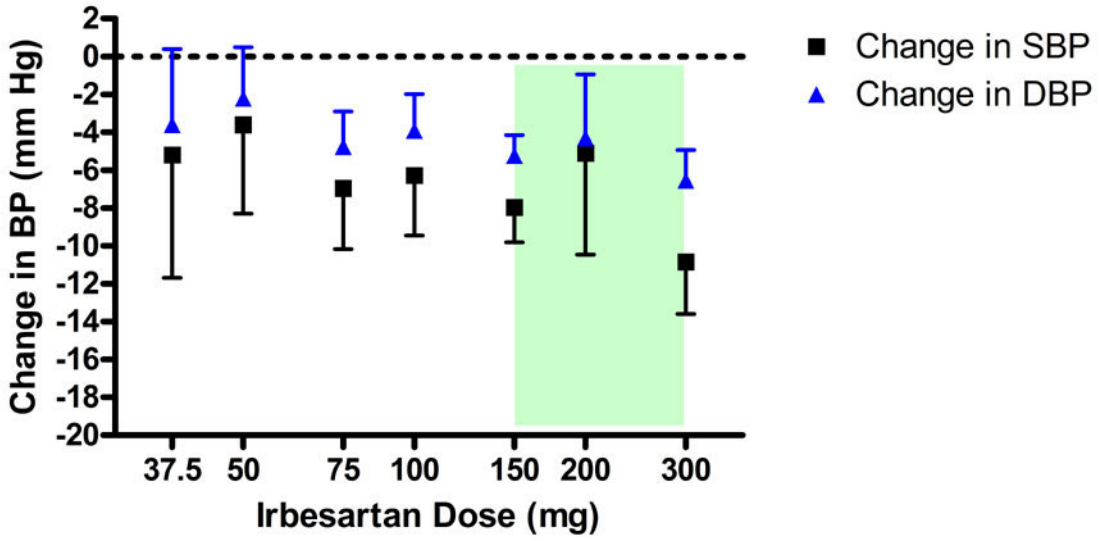



Based on the available trial evidence, 600 mg/day significantly reduces blood pressure compared with placebo but not enough doses were tested to determine whether 600 mg/day is the lowest effective dose or whether it achieves near maximal blood pressure lowering efficacy. Thus the true near maximal blood pressure lowering efficacy of eprosartan cannot be estimated and a meaningful dose-response curve cannot be constructed. The best estimate of the near maximal blood pressure lowering efficacy of eprosartan, 600 to 1200 mg/day, is -6.79 (95% CI -9.35, -4.22) mm Hg for SBP and -5.12 (95% CI -6.64, -3.60) mm Hg for DBP.

### 3.2.4.3 Dose-ranging BP lowering efficacy of irbesartan

Nine of the included studies assessed irbesartan, encompassing a dose range of 37.5 to 300 mg/day (Figure 3.6).

**Figure 3.6: Log dose-response curve of irbesartan 37.5 - 300 mg/day (Shaded area represents manufacturer's recommended dose range)**




Eight studies were funded by the manufacturer of irbesartan and one trial studied irbesartan as a comparator against the renin inhibitor, aliskiren [40]. All doses except 37.5 and 50 mg/day exhibited a statistically significant reduction in blood pressure compared with placebo. Using indirect comparisons, there was no statistically significant difference between any of the doses tested. The lowest effective dose was 75 mg/day, which is half of the manufacturer's recommended starting dose.

In the 150 mg/day group, there was statistically significant heterogeneity in change in DBP ($Chi^2$ = 12.02, p = 0.03, $I^2$ = 58.4%). The random effects model still demonstrated a statistically significant difference from placebo. The heterogeneity was resolved, but the overall DBP effect estimate was not affected, by removing one trial [38] that reported a larger reduction in DBP (-10.2 mm Hg) than the other trials in the 150 mg/day group (weighted mean: -5.01 mm Hg). A possible explanation for the exaggerated effect estimate could be the higher baseline DBP level (107 mm Hg) versus the other trials (weighted mean: 100 mm Hg). Also, an oscillometric device was utilized

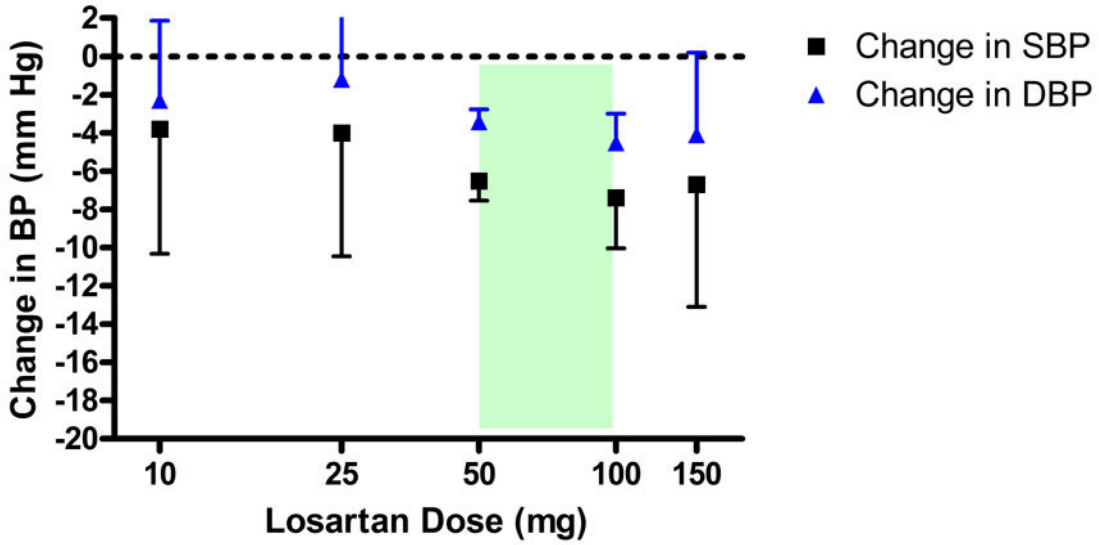
in this trial to measure blood pressure in the supine position whereas sitting blood pressure was measured with a mercury sphygmomanometer in the other trials.

The best estimate of the near maximal blood pressure lowering efficacy occurring at 75 to 300 mg/day is -7.91 (95% CI -9.16, -6.67) mm Hg for SBP and -5.09 (95% CI -5.82, -4.36) mm Hg for DBP.

#### 3.2.4.4 Dose-ranging BP lowering efficacy of losartan

Twelve of the included trials assessed losartan over a dose range of 10 to 150 mg/day (Figure 3.7).

**Figure 3.7: Log dose-response curve of losartan 10 - 50 mg/day (Shaded area represents manufacturer's recommended dose range)**




Losartan at 10 and 25 mg/day did not statistically significantly lower blood pressure compared with placebo. The lowest effective dose was 50 mg/day, the manufacturer's recommended starting dose. The 50 mg/day dose was also the lowest dose with near maximal blood pressure lowering efficacy since indirect comparison of the results for 50, 100 and 150 mg/day doses showed no statistical difference in blood pressure lowering effect.

There was statistically significant heterogeneity in the 50 mg/day estimate of DBP reduction ($Chi^2 = 19.93$, $p = 0.02$, $I^2 = 54.8\%$) but the random effects model still showed a statistically significant reduction in DBP compared with placebo. Since the

heterogeneity could not be explained by differences in baseline demographics of the patients between trials, another possible explanation could be the source of funding. Losartan was the only ARB used as an active comparator in trials as frequently as it was the primary drug of investigation. Five trials [46,48,50,52,53] were sponsored by the manufacturer of losartan and four trials [29,49,51] were funded by other manufacturers who compared losartan against their drugs. Sensitivity analyses of the funding source did not change the results; the heterogeneity was still statistically significant when analyzing each group of trials and the DBP effect size of -3.3 mm Hg versus placebo was unchanged.

The best estimate of the near maximal blood pressure lowering efficacy of losartan at 50 to 150 mg/day is -6.64 (95% CI -7.59, -5.68) mm Hg for SBP and -3.59 (95% CI -4.17, -3.00) mm Hg for DBP. Funnel plots of the trials at losartan 50 mg/day and above suggest that publication bias is likely since there is an absence of small trials with results to the right of the line for SBP (Figure 3.8) and DBP (Figure 3.9). Thus, the best estimate of the near maximal blood pressure lowering efficacy of losartan is likely an overestimate of the true effect size.

**Figure 3.8: Funnel plot of standard error against effect estimate of change in SBP for losartan 50 to 150 mg/day**

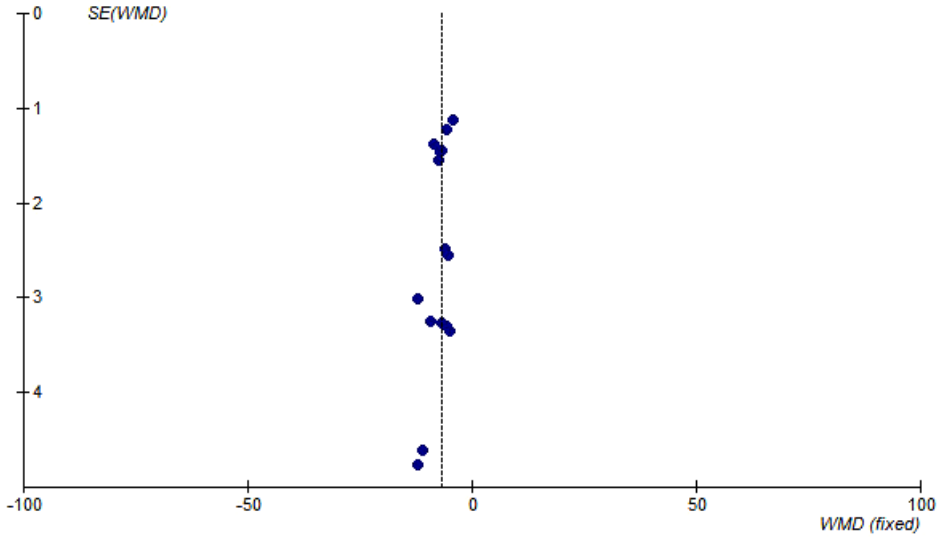
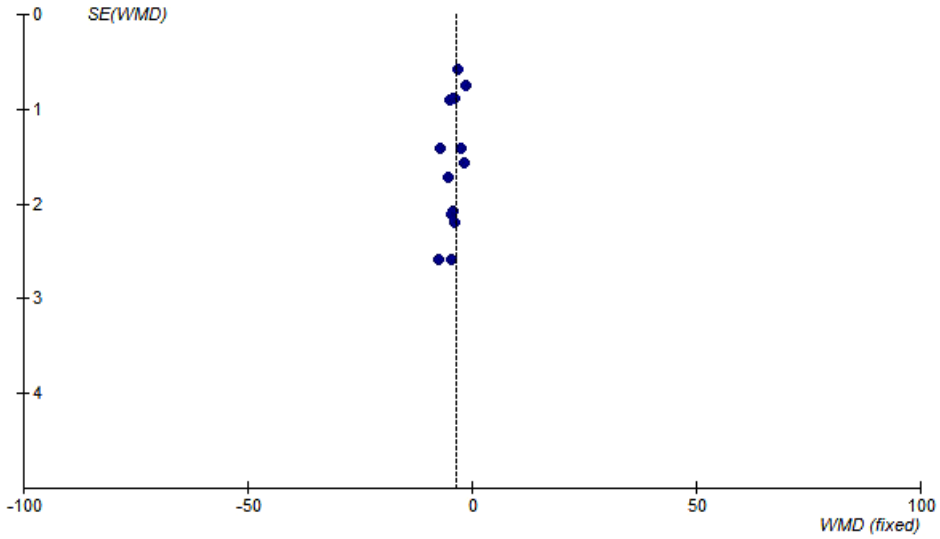


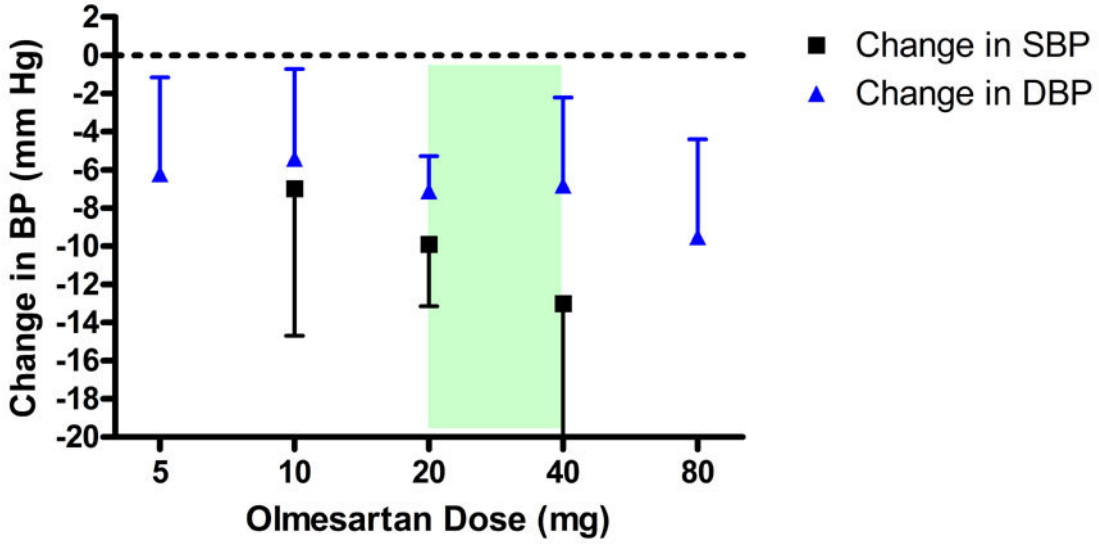
**Figure 3.9: Funnel plot of standard error against effect estimate of change in DBP for losartan 50 to 150 mg/day**




### 3.2.4.5 Dose-ranging BP lowering efficacy of olmesartan

Two of the included trials [58,59] evaluated the SBP and DBP lowering efficacy of olmesartan 10 to 40 mg/day and one additional trial [60] reported the change in DBP only at 5, 20 and 80 mg/day (Figure 3.10). All three trials were sponsored by the manufacturer of olmesartan.

**Figure 3.10: Log dose-response curve of olmesartan 5 - 80 mg/day (Shaded area represents manufacturer's recommended dose range)**



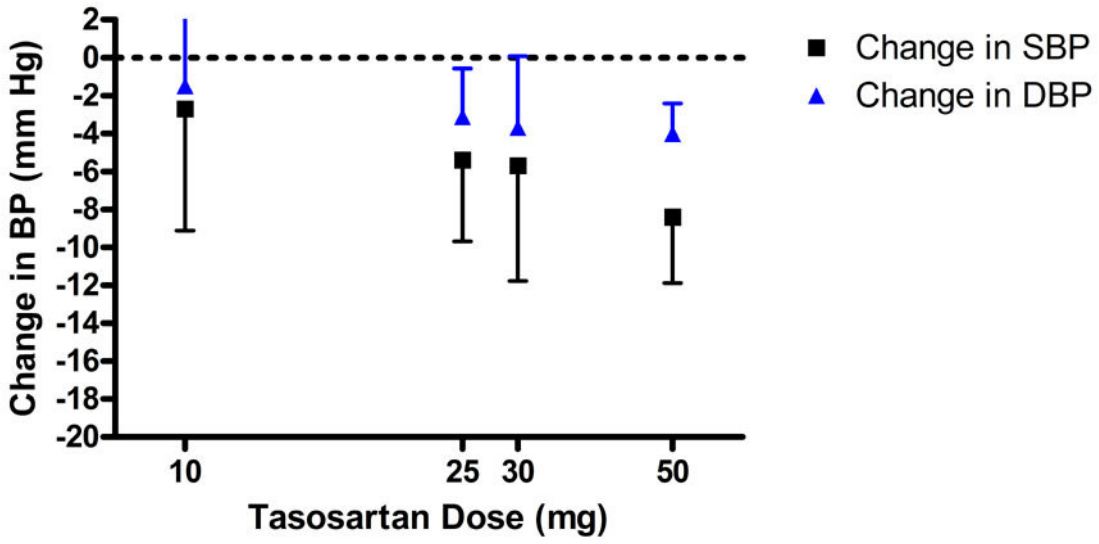
All doses resulted in statistically significant reductions in DBP compared with placebo. For SBP, only the 20 and 40 mg/day doses significantly reduced SBP over placebo. Based on the available evidence, the lowest effective dose for SBP and DBP was 20 mg/day. The lowest effective dose may be achieved at 10 mg/day but there are not enough SBP data available to demonstrate this, as reflected by the wide confidence limits.

It was unclear if the 20 to 80 mg/day dose range reflects the plateau of the dose-response curve because there were few studies at each dose above 20 mg/day. Thus, the true near maximal blood pressure lowering efficacy cannot be estimated. An estimate using the available trial data at 20 to 40 mg/day is -10.39 (95% CI -13.36, -7.42) mm Hg for SBP and -7.31 (95% CI -8.92, -4.40) mm Hg for DBP.

#### 3.2.4.6 Dose-ranging BP lowering efficacy of tasosartan

Tasosartan was never marketed in North America after evidence of hepatotoxicity so dosing information is not available. Three of the included studies assessed tasosartan 10 to 50 mg/day (Figure 3.11).

**Figure 3.11: Log dose-response curve of tasosartan 10 - 50 mg/day**




The 10 mg/day group did not have a statistically significant difference from placebo. The lowest effective dose was 25 mg/day. The 30 mg/day dose did not

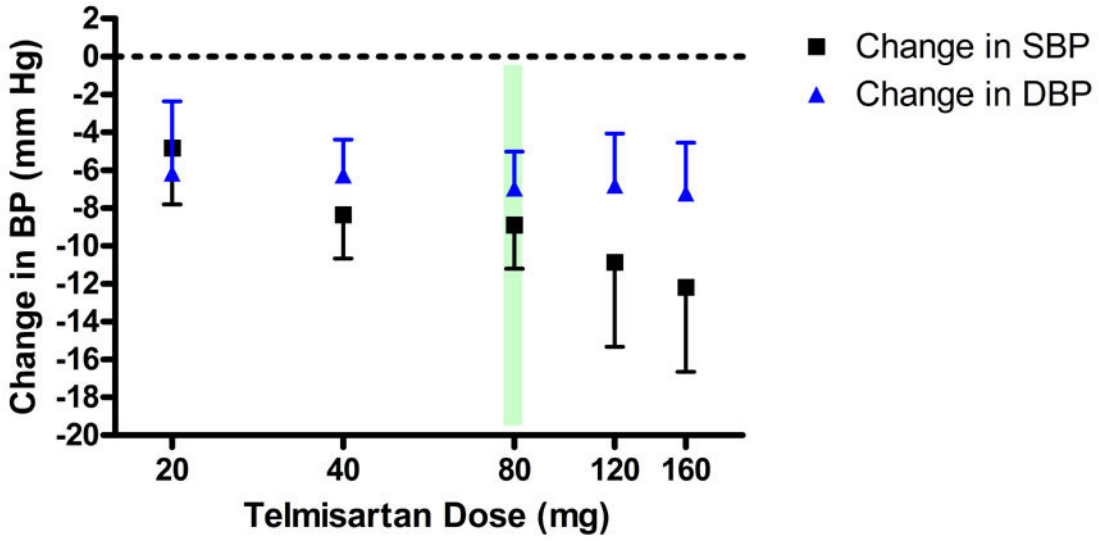
demonstrate a statistically significant difference compared with placebo but this is likely due to the paucity of data.

There was no statistically significant difference between 25 and 50 mg/day for SBP and DBP lowering efficacy. The best estimate of the near maximal blood pressure lowering efficacy for 25 to 50 mg/day is -6.95 (95% CI -9.42, -4.48) mm Hg for SBP and -3.74 (95% CI -5.01, -2.47) mm Hg for DBP.

### 3.2.4.7 Dose-ranging BP lowering efficacy of telmisartan

The blood pressure lowering efficacy of telmisartan was assessed by 6 included trials (Figure 3.12). Five trials were sponsored by the manufacturer of telmisartan and one trial [51] did not report the source of funding.

**Figure 3.12: Log dose-response curve of telmisartan 20 - 160 mg/day (Shaded area represents manufacturer's recommended dose)**




The manufacturer only recommends a single dose of 80 mg/day in healthy patients (a starting dose of 40 mg is recommended in patients with hepatic impairment) and if additional blood pressure reduction is required, they recommend a thiazide diuretic be added [79]. Based on the available evidence, the lowest effective dose was achieved at 20 mg/day.

Although all doses resulted in a statistically significant difference from placebo, there was no statistically significant difference between any of the doses assessed using

indirect comparisons. The best estimate of the near maximal blood pressure lowering efficacy of telmisartan across all doses (20 to 160 mg/day) is -8.38 (95% CI -9.69, -7.07) mm Hg for SBP and -6.69 (95% CI -7.74, -5.64) mm Hg for DBP.

A funnel plot of standard error versus effect size for all telmisartan doses demonstrates asymmetry, with an absence of smaller trials with effects to the right of the line (Figures 3.13 - 3.14). This suggests the presence of publication bias and the estimate of the blood pressure lowering efficacy of telmisartan is likely an overestimate of the true effect size.

**Figure 3.13: Funnel plot of standard error against effect estimate of change in SBP for telmisartan 20 to 160 mg/day**

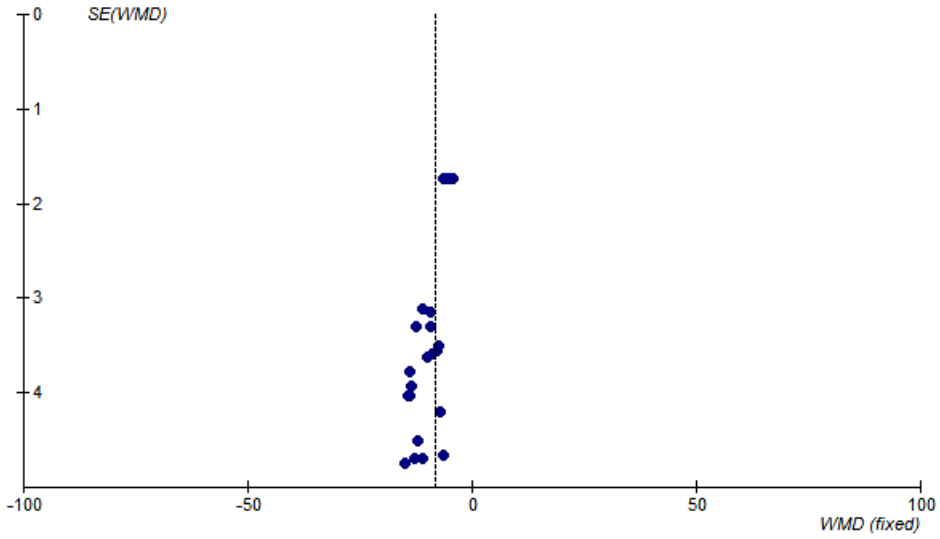
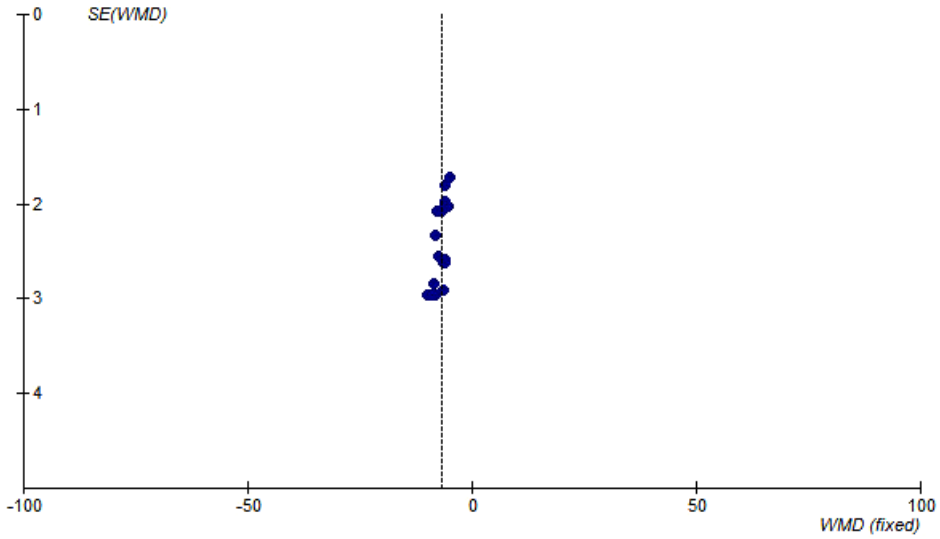


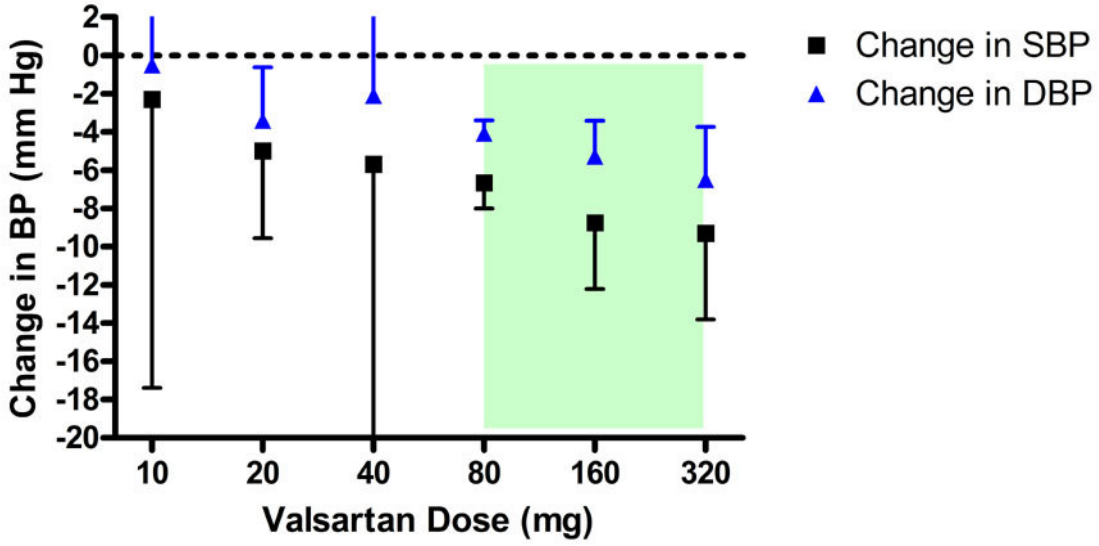
**Figure 3.14: Funnel plot of standard error against effect estimate of change in DBP for telmisartan 20 to 160 mg/day**




### 3.2.4.8 Dose-ranging BP lowering efficacy of valsartan

Nine of the included trials assessed valsartan, encompassing a dose range of 10 mg/day to 320 mg/day (Figure 3.15).

**Figure 3.15: Log dose-response curve of valsartan 10 - 320 mg/day (Shaded area represents manufacturer's recommended dose)**



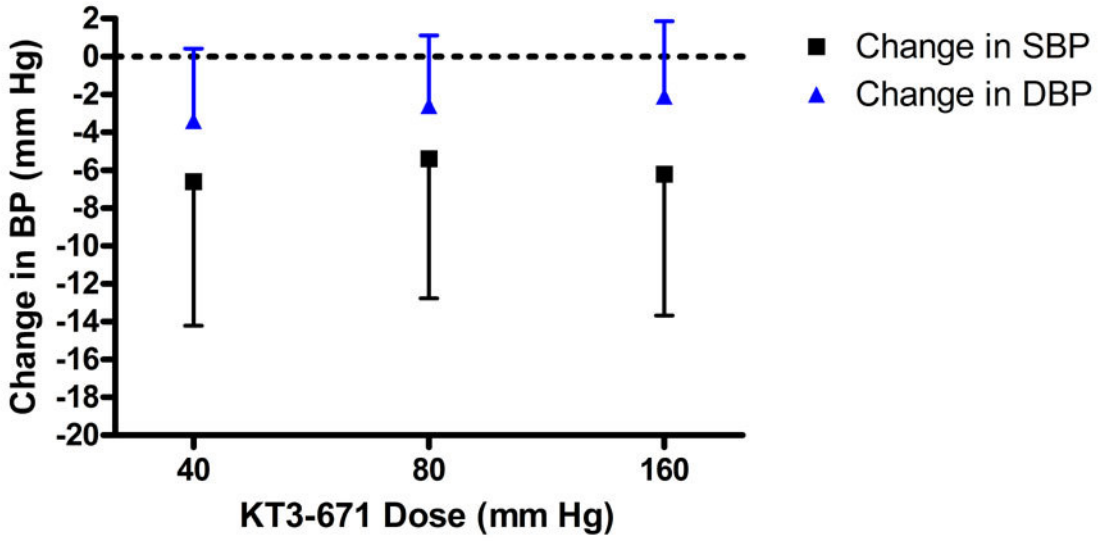
Eight trials were funded by the manufacturer and one trial [31] did not report the source of funding. Valsartan at 10 and 40 mg/day did not statistically significantly lower blood pressure compared with placebo. However, there is much uncertainty in the 40 mg/day efficacy estimate since it is based on one small trial, as reflected by the wide confidence limits.

Valsartan 20 mg/day is the lowest effective dose. Using indirect comparisons, there was a statistically significant difference in effect sizes between 20 and 80 mg/day. Thus the lowest dose with near maximal blood pressure lowering efficacy is 80 mg/day, the manufacturer's recommended starting dose. The weighted mean efficacy estimate of the maximum recommended dose of 160 mg/day and 320 mg/day did not result in a statistically significant difference from 80 mg/day, using indirect comparisons. Based on the available evidence, the best estimate of the near maximal blood pressure lowering efficacy for valsartan at 80 to 320 mg/day is -7.10 (95% CI -8.30, -5.90) mm Hg for SBP and -4.34 (95% CI -4.96, -3.72) mm Hg for DBP.

#### 3.2.4.9 Dose-ranging BP lowering efficacy of KT3-671

Only 1 trial [78] assessed KT3-671, an experimental drug manufactured in Japan, and for this reason there is much uncertainty in the results, reflected by the wide confidence limits for all doses studied (Figure 3.16).

**Figure 3.16: Log dose-response curve of KT3-671 40 - 160 mg/day**



Based on the available evidence, the overall best estimate of the blood pressure lowering efficacy of KT3-671 40 to 160 mg/day is -6.05 (95% CI -10.38, -1.73) mm Hg and -2.71 (95% CI -4.92, -0.50) mm Hg for SBP and DBP, respectively.

### 3.2.5 Summary of the BP lowering efficacy of ARBs

Table 3.12 provides an overview of the lowest effective dose, the lowest dose with near maximal blood pressure lowering and the near maximal blood pressure lowering effect of each ARB studied in this review.

**Table 3.12: Summary of the BP lowering efficacy of ARBs**

| ARB | Lowest effective dose (mg/day) | Lowest dose with near max. BP lowering (mg/day) | Near maximal trough SBP lowering (mm Hg), 95% CI | Near maximal trough DBP lowering (mm Hg), 95% CI |
|---|---|---|---|---|
| candesartan | 4 | 4 | -8.93 (-11.37, -6.50) | -4.92 (-6.47, -3.36) |
| eprosartan | 600 | 600 | -6.79 (-9.35, -4.22) | -5.43 (-6.47, -4.40) |
| irbesartan | 75 | 75 | -5.58 (-7.84, -3.32) | -3.50 (-4.40, -2.60) |
| losartan | 50 | 50 | -8.66 (-10.48, -6.84) | -4.80 (-5.81, -3.79) |
| olmesartan | 20 | 20 | -10.39 (-13.36, -7.42) | -7.31 (-8.92, -4.40) |
| tasosartan | 25 | 25 | -9.30 (-14.83, -3.78) | -5.76 (-9.44, -2.07) |
| telmisartan | 20 | 40 | -8.00 (-10.14, -5.85) | -4.76 (-5.92, -3.60) |
| valsartan | 20 | 80 | -8.45 (-11.99, -4.91) | -4.38 (-6.29, -2.46) |
| KT3-671 | Not estimable | Not estimable | -7.09 (-9.56, -4.61) | -5.02 (-6.22, -3.82) |

The lowest effective dose is defined as the lowest dose for which there is a statistically significant difference from placebo. The lowest dose with near maximal blood pressure lowering efficacy is defined as the dose that demonstrates a statistically significantly greater response than doses below it, but does not exhibit a statistically significant difference in effect size compared with higher doses. If there was any discrepancy between SBP and DBP, SBP was used to make the dose determination.

Trough blood pressure data were pooled for the ARBs by categorizing individual doses as proportions of the manufacturer's maximum recommended daily dose (Max), ranging from 1/8 Max to 2 Max (Figures 3.17 - 3.22).

**Figure 3.17: BP lowering efficacy of ARBs at 1/8 Max**

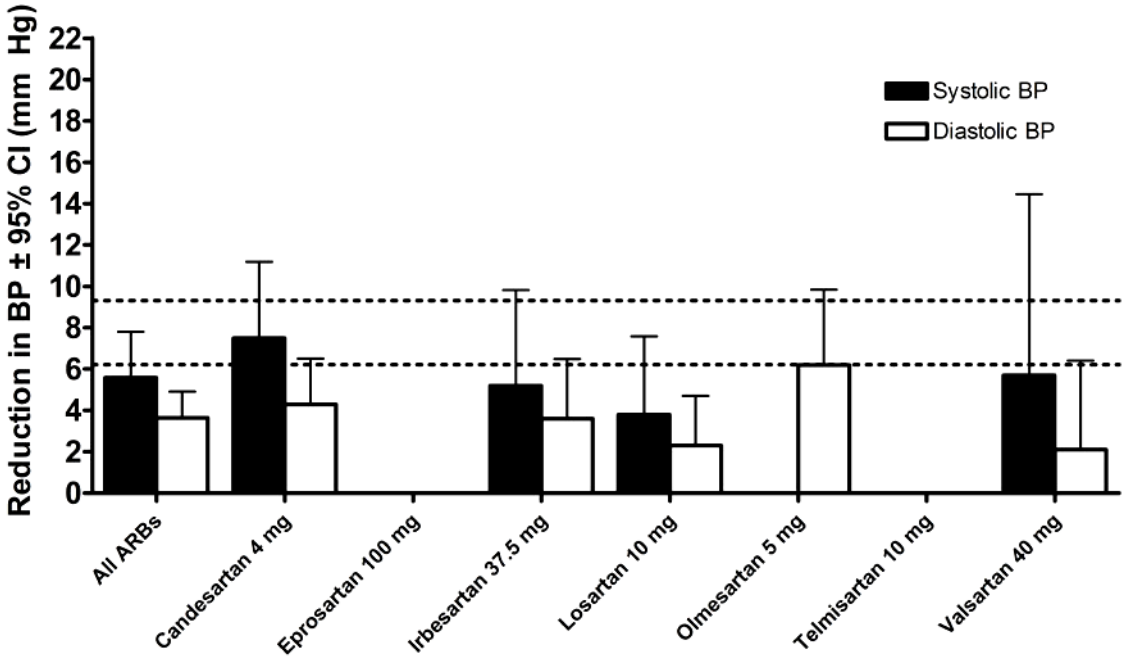



**Figure 3.18: BP lowering efficacy of ARBs at 1/4 Max**

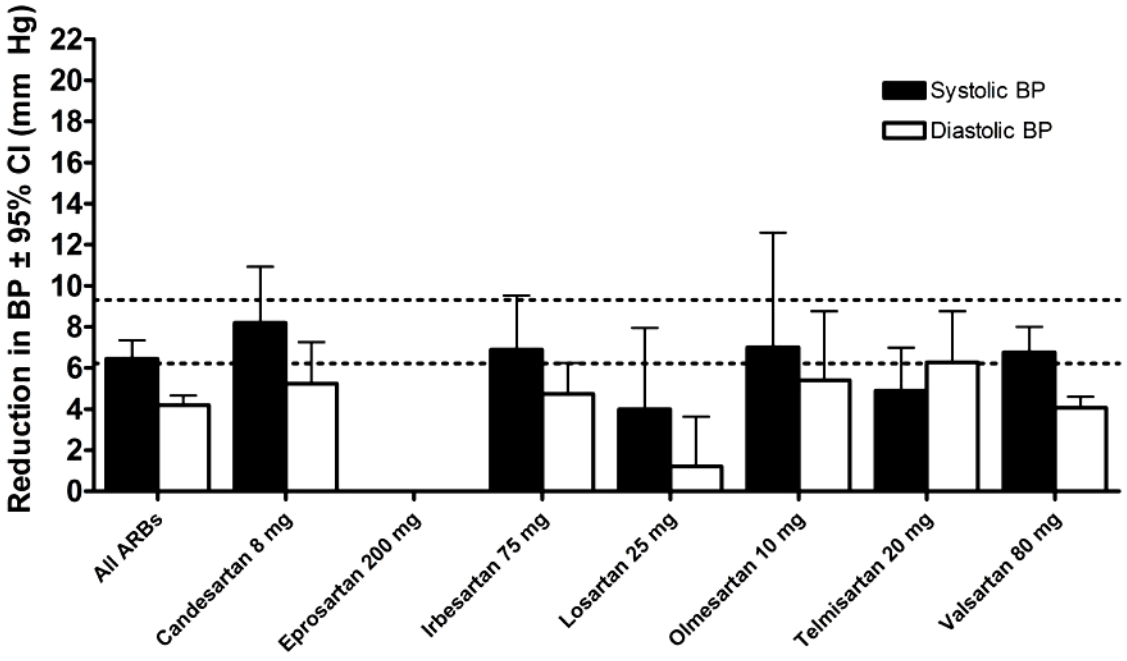


**Figure 3.19: BP lowering efficacy of ARBs at 1/2 Max**

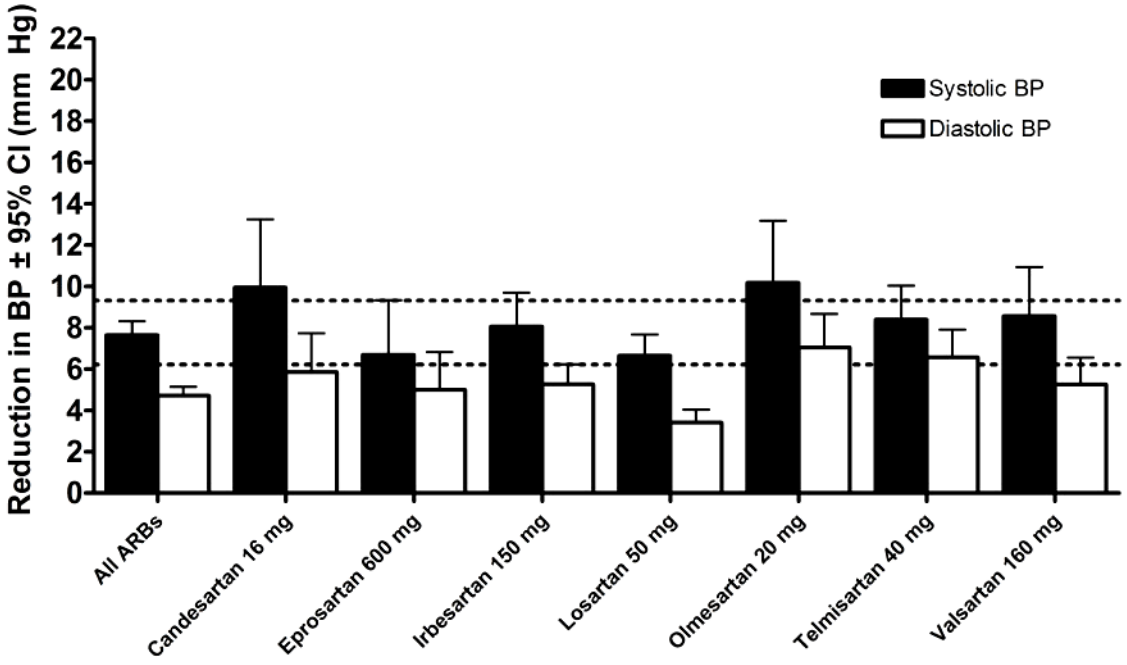



**Figure 3.20: BP lowering efficacy of ARBs at Max**

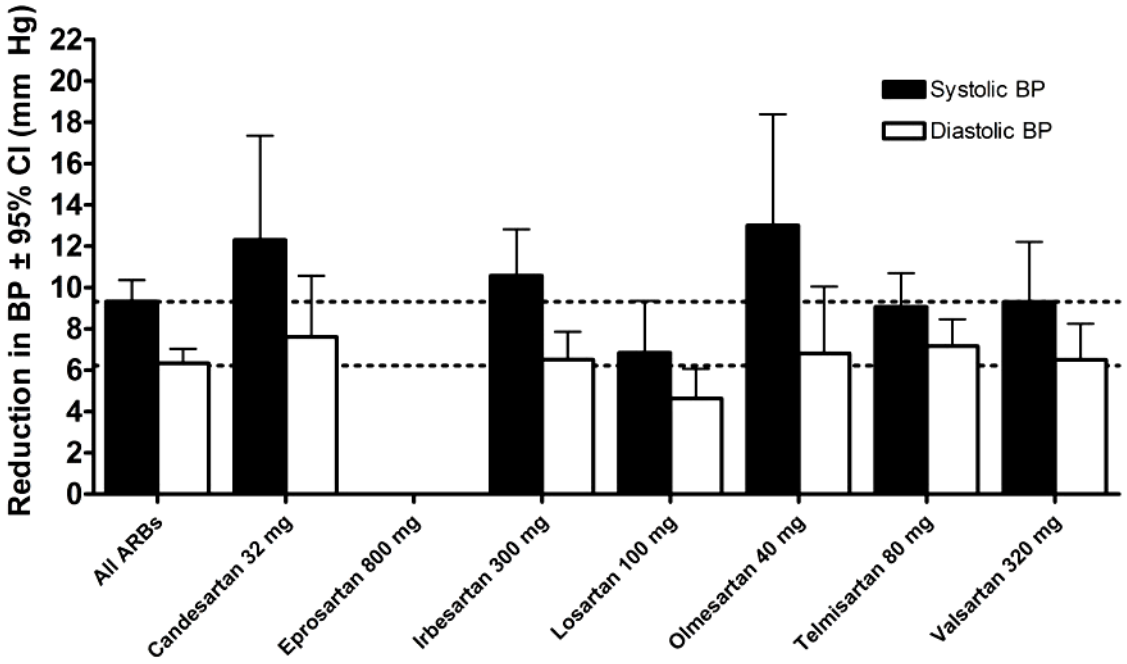


**Figure 3.21: BP lowering efficacy of ARBs at 1.5 Max**

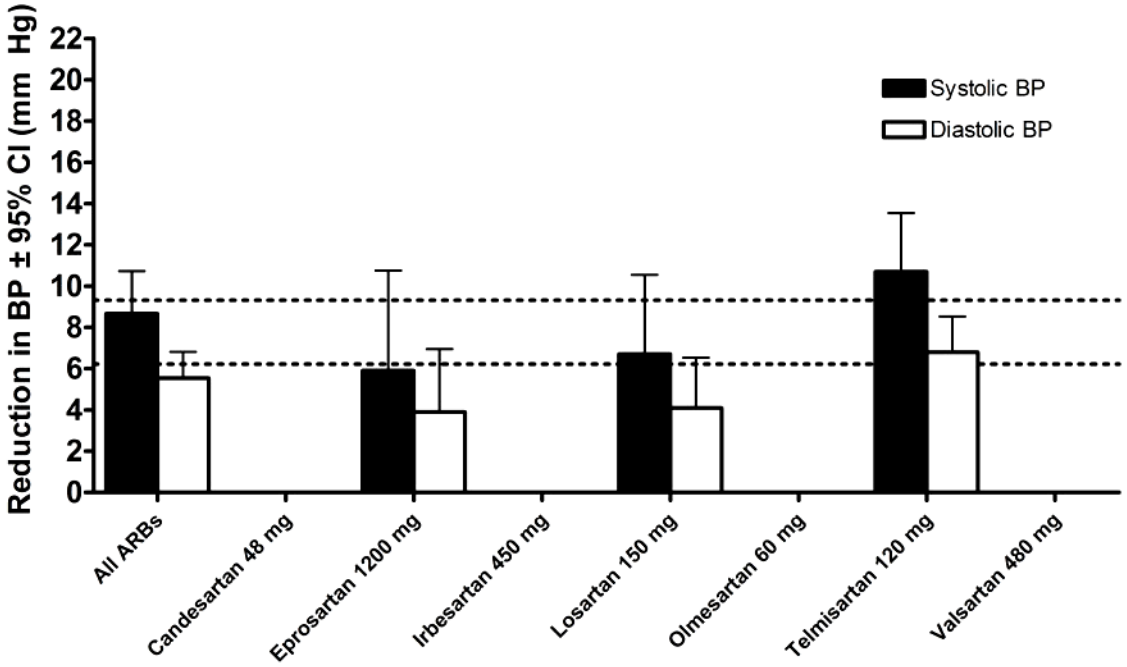
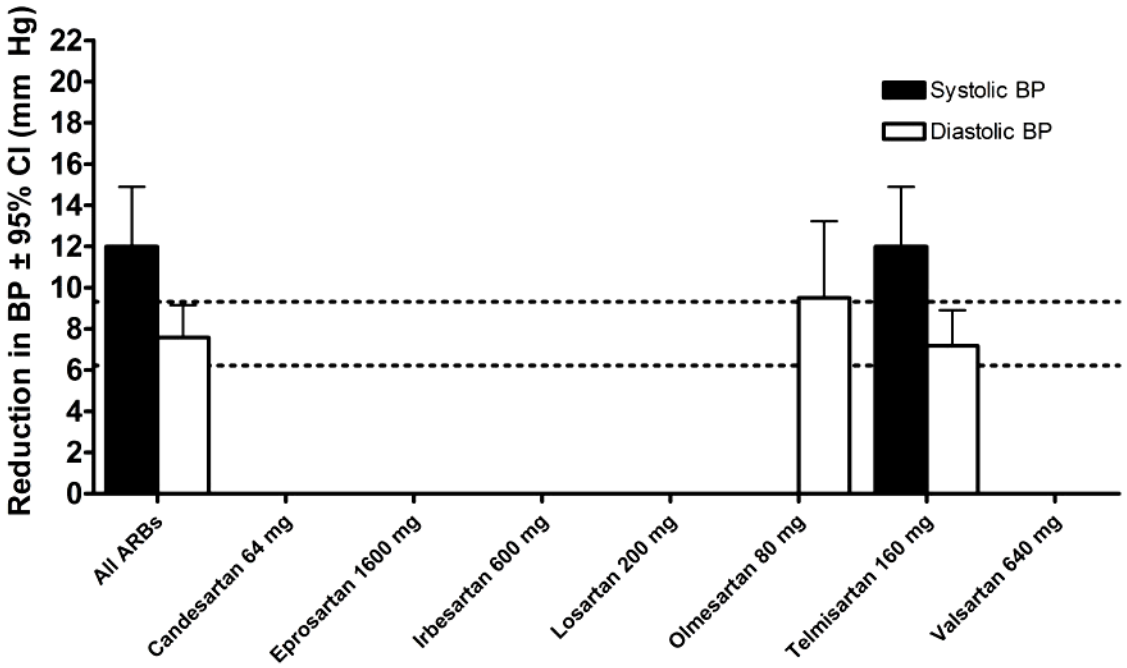
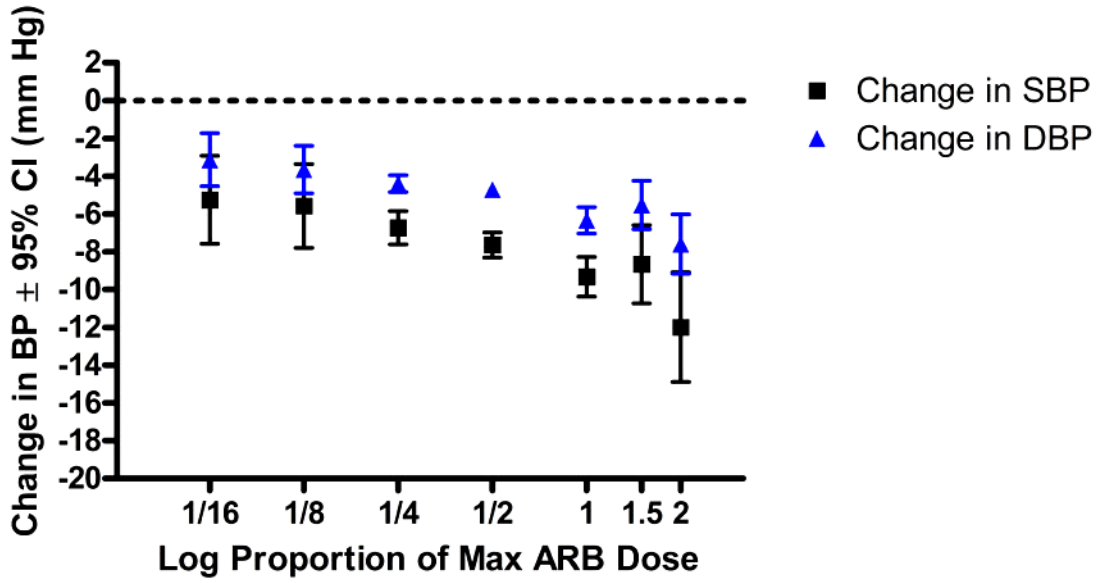



**Figure 3.22: BP lowering efficacy of ARBs at 2 Max**



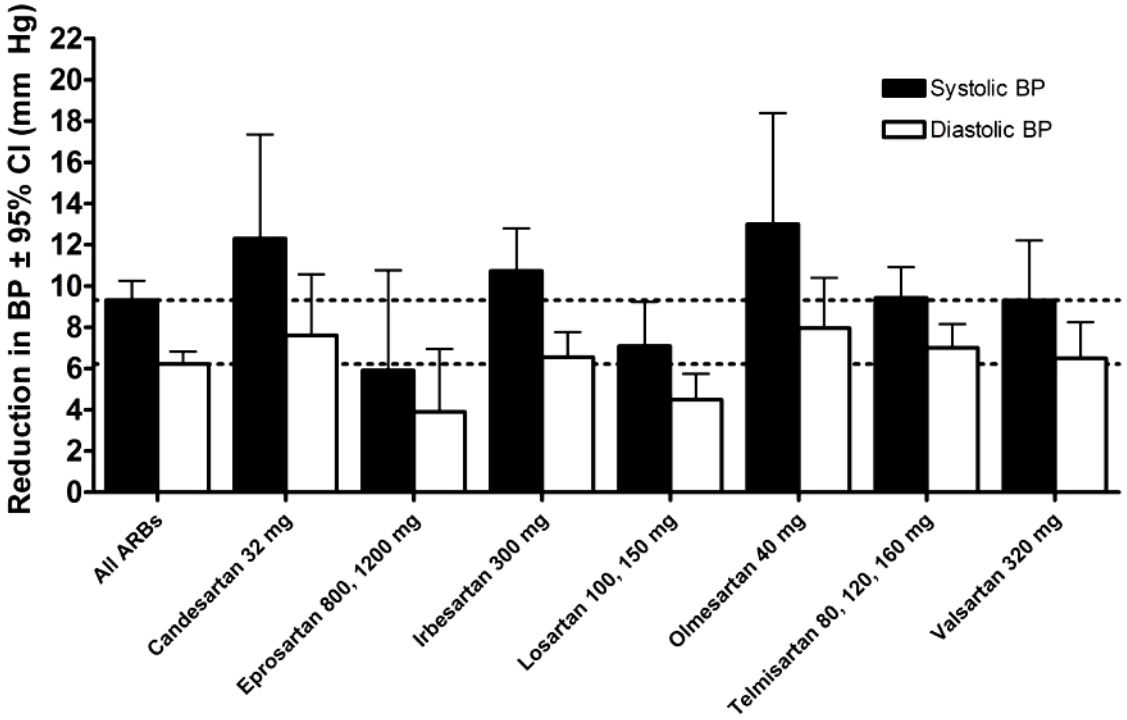
A dose-response exists, with a statistically significant difference between 1/2 Max and Max. There was no statistically significant difference in blood pressure lowering between Max and higher doses (Figure 3.23).

**Figure 3.23: Log dose-response curve of ARBs according to proportions of Max**




As a class, the best estimate of the near maximal blood pressure lowering for ARBs is -9.31 (95% CI -10.25, -8.37) mm Hg for SBP and -6.22 (95% CI -6.82, -5.62) mm Hg for DBP (Figure 3.24).

**Figure 3.24: Near maximal blood pressure lowering efficacy of ARBs**




### 3.2.6 Analysis of publication bias

#### 3.2.6.1 Funnel plots

In order to test for the possibility of publication bias in the ARB review, funnel plots were created of the trough SBP and DBP lowering effects of all doses of maximum recommended and higher. The funnel plots of the near maximal SBP and DBP lowering efficacy of ARBs (i.e. at Max and above) suggest asymmetry, which appears to be due to an absence of smaller, negative-result trials (Figures 3.25 - 3.26). However, there are not very many trials at Max and higher doses to adequately assess whether publication bias is likely.

**Figure 3.25: Funnel plot of near maximal change in trough SBP for ARBs at Max and higher doses**

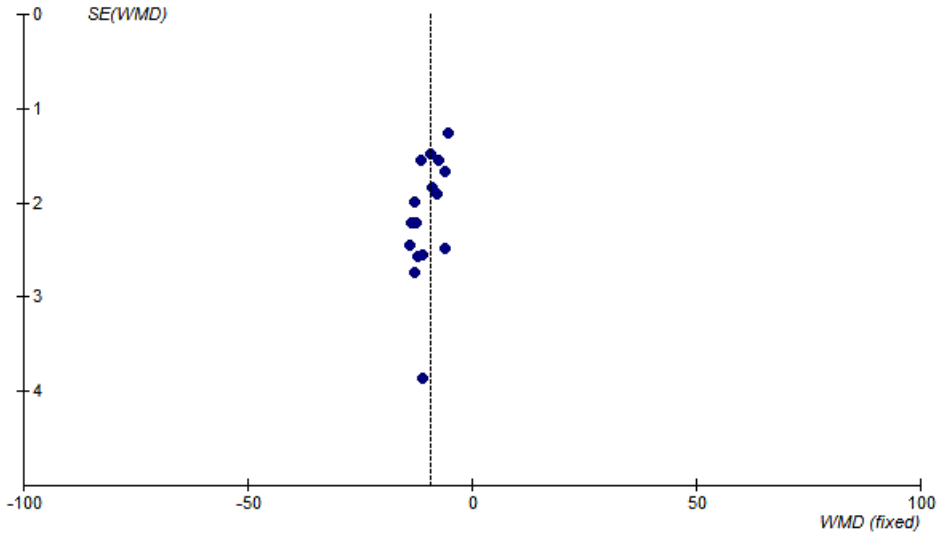
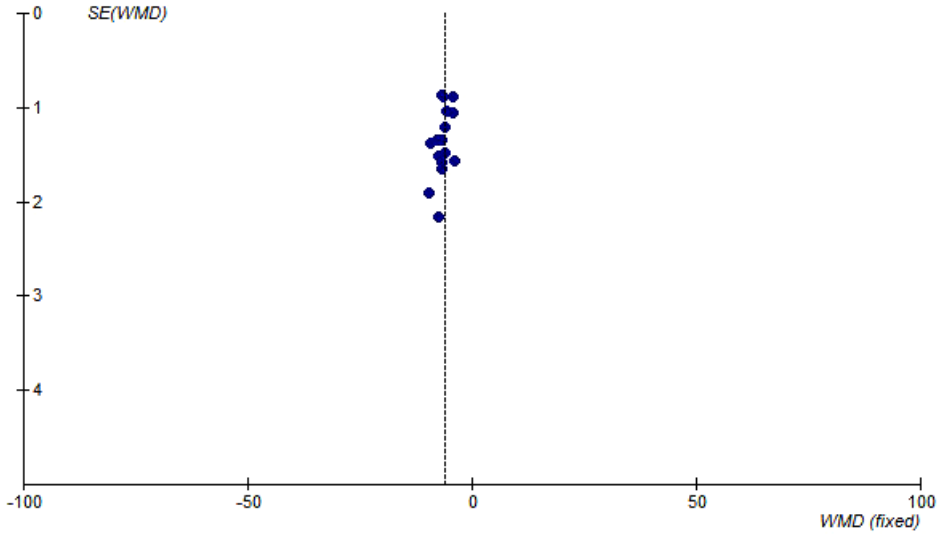



**Figure 3.26: Funnel plot of near maximal change in trough DBP for ARBs at Max and higher doses**




Since most of the available efficacy data for ARBs are at 1/2 Max, the funnel plots of this dosage level were also analyzed and they also demonstrate asymmetry, with an absence of negative-result trials of small to medium size (Figures 3.27 - 3.28).

**Figure 3.27: Funnel plot of near maximal change in trough SBP for ARBs at 1/2 Max**

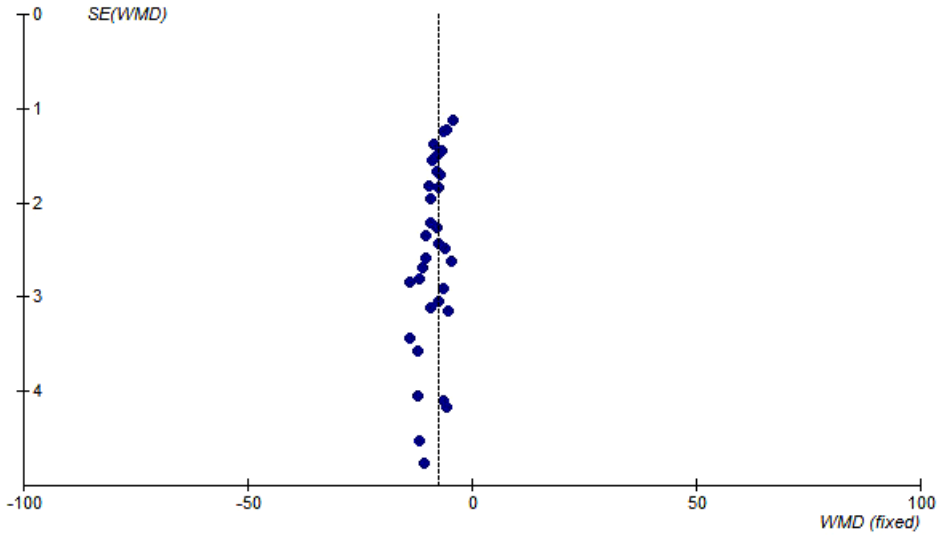
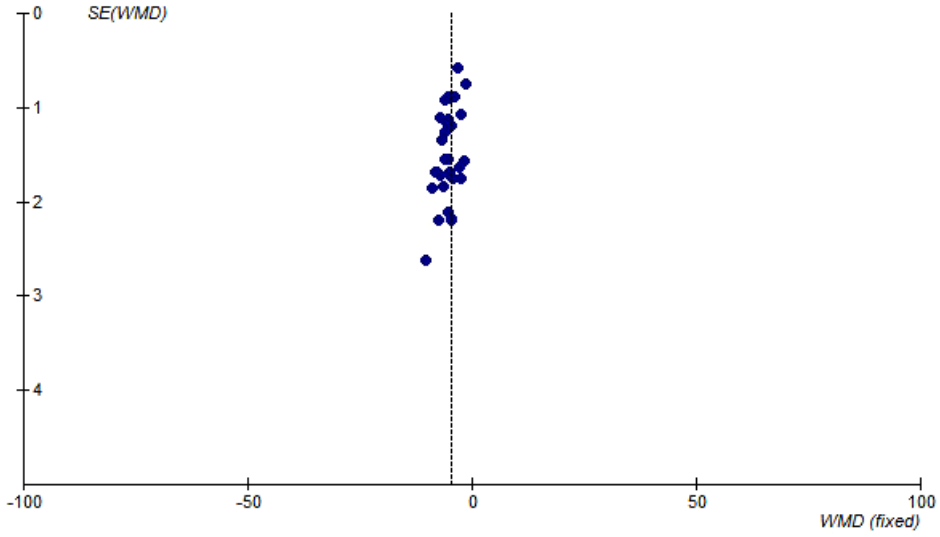



**Figure 3.28: Funnel plot of near maximal change in trough DBP for ARBs at 1/2 Max**



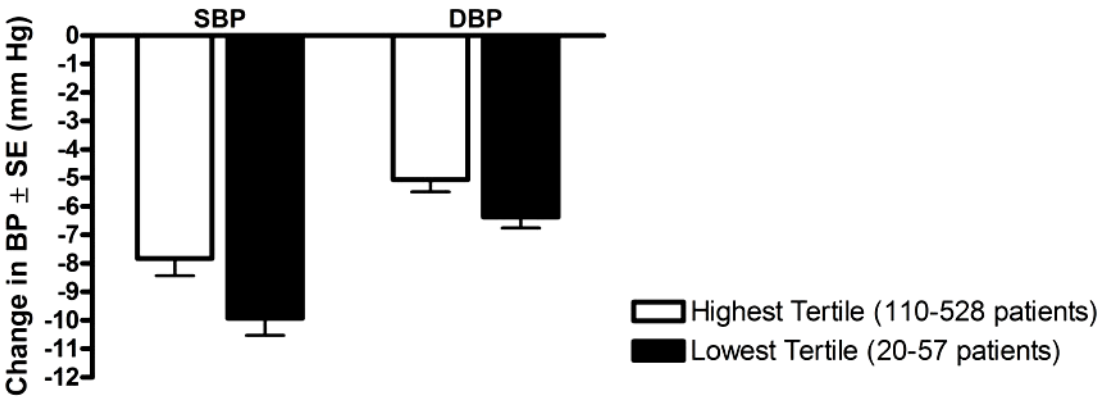

### 3.2.6.2 Tertile analysis based on trial size

In order to further test the possibility of publication bias, a post-hoc tertile analysis of ARB trials was performed to determine if the trial size had an impact on the magnitude of reported blood pressure lowering. Trials that reported trough blood pressure at Max and above were divided into tertiles according to the sample size in the active

treatment arms. The lowest, middle and highest tertiles represented the smallest, medium-sized and largest trials, respectively. Using the indirect method, the mean effect size of the largest trials (highest tertile) was compared with that of the smallest trials (lowest tertile).

In this case, there were statistically significant differences in the magnitude of SBP (p = 0.02) and DBP (p = 0.03) reduction between the largest (n=110-528 patients) and smallest (n=20-57 patients) trials. The smallest trials reported 2.1/1.3 mm Hg greater mean reduction in SBP (p = 0.02)/DBP (p = 0.03) versus the largest trials (Figure 3.29).

**Figure 3.29: Post-hoc tertile analysis of the effect of trial size on reported trough BP lowering**




### 3.2.6.3 Tertile analysis based on publication year

Another possible source of bias in this review is that introduced because the patients chosen for the trial were already known to respond well to ARBs. If this were occurring, it was hypothesized that there would be little possibility for this to happen in the earliest published trials and that it would be more likely to occur in later published trials when use of the class was more common. A post-hoc tertile analysis was done to determine the effect of the year of publication of trials on the blood pressure lowering effect. The mean effect size of the latest tertile (2002-2005) was compared with that of the earliest tertile (1995-1998) using the indirect method and there was no statistically significant difference for SBP (p=0.8) or DBP (p=1.0) between the tertiles.

### 3.2.7 Blood pressure variability

#### 3.2.7.1 Systolic versus diastolic blood pressure variability

The variability of blood pressure at both baseline and endpoint was reported for 7 (15%) of the included trials. In Table 3.13, the number of observations represents the number of active treatment arms in these 7 trials.

**Table 3.13: Variability of systolic and diastolic BP at end of treatment**

| | | ARB | Placebo |
|---|---|---|---|
| SBP | Weighted mean SD | 16.9 | 16.0 |
| | SD of weighted mean SD | 3.8 | 2.2 |
| | Weighted mean SBP | 147.3 | 156.3 |
| | Weighted mean coefficient of variation (CV) | 11.5 | 10.3 |
| | SD of weighted mean CV | 2.4 | 1.6 |
| | Number of observations | 10 | 6 |
| DBP | Weighted mean SD | 8.1 | 7.8 |
| | SD of weighted mean SD | 1.7 | 1.6 |
| | Weighted mean DBP | 92.9 | 98.0 |
| | Weighted mean CV | 8.7 | 8.0 |
| | SD of weighted mean CV | 1.9 | 1.8 |
| | Number of observations | 10 | 6 |
| t-test | SD of SBP vs. SD of DBP | $p < 0.0001$ | $p < 0.0001$ |
| t-test | CV SBP vs. CV DBP | $p = 0.0070$ | $p = 0.0055$ |

Forty (87%) of the studies had diastolic hypertension entry criteria, 3 (6.5%) trials had systo-diastolic hypertension entry criteria [51,65,74], and 3 (6.5%) trials had isolated systolic hypertension entry criteria [36,45,64].

The weighted mean standard deviations for SBP and DBP were compared in order to determine whether SBP varies to the same degree as DBP. For both the ARB and placebo groups, the absolute variability of SBP is statistically significantly greater than that of DBP (Table 3.13). The coefficient of variation in SBP was also significantly greater than the coefficient of variation in DBP for both the ARB and placebo groups.

### 3.2.7.2 ARBs versus placebo

As shown in Table 3.13, the weighted mean endpoint SD of SBP was 16.9 mm Hg for the ARB group and 16.0 mm Hg for the placebo group (p = 0.6). The weighted mean SD of DBP was 8.1 mm Hg for the ARB group and 7.8 mm Hg for the placebo group (p = 0.7). There was no statistically significant difference in endpoint blood pressure variability between the ARB and placebo groups.

### 3.2.7.3 The effect of blood pressure entry criteria on variability

The included trials were categorized according to blood pressure entry criteria used: 1) diastolic hypertension; 2) systolic hypertension; and 3) systo-diastolic hypertension. The weighted mean baseline standard deviations of these three trial categories were compared in order to determine the effect of blood pressure entry criteria on blood pressure variability at baseline (Table 3.14).

**Table 3.14: Baseline standard deviations of BP according to entry criteria**

| | | Trials with DBP entry criteria only | Trials with SBP entry criteria only | Trials with SBP and/or DBP entry criteria |
|---|---|---|---|---|
| | Number of trials | 27 | 3 | 3 |
| SBP | Weighted mean SD at baseline (mm Hg) | 14.2 | 9.2 | 13.0 |
| | SD of weighted mean SD (mm Hg) | 1.8 | 1.7 | 2.3 |
| | Number of observations | 76 | 8 | 8 |
| DBP | Weighted mean SD at baseline (mm Hg) | 4.7 | 4.6 | 5.2 |
| | SD of weighted mean SD (mm Hg) | 1.1 | 0.7 | 0.4 |
| | Number of observations | 78 | 8 | 8 |

Trials with systolic hypertension entry criteria had statistically significantly lower baseline SBP variability than trials with trials with entry criteria based on elevated DBP alone ($p < 0.0001$) or both elevated SBP and DBP (p = 0.002). There was no statistically significant difference between all categories for variability in DBP at baseline.

### 3.2.7.4 Baseline versus endpoint variability

Table 3.15 shows the comparisons of standard deviations of blood pressure at baseline and endpoint for trials with DBP entry criteria. The variability of SBP at endpoint was statistically significantly higher than at baseline for both the ARB and placebo groups. The DBP variability at endpoint was also significantly higher than at baseline in both groups.

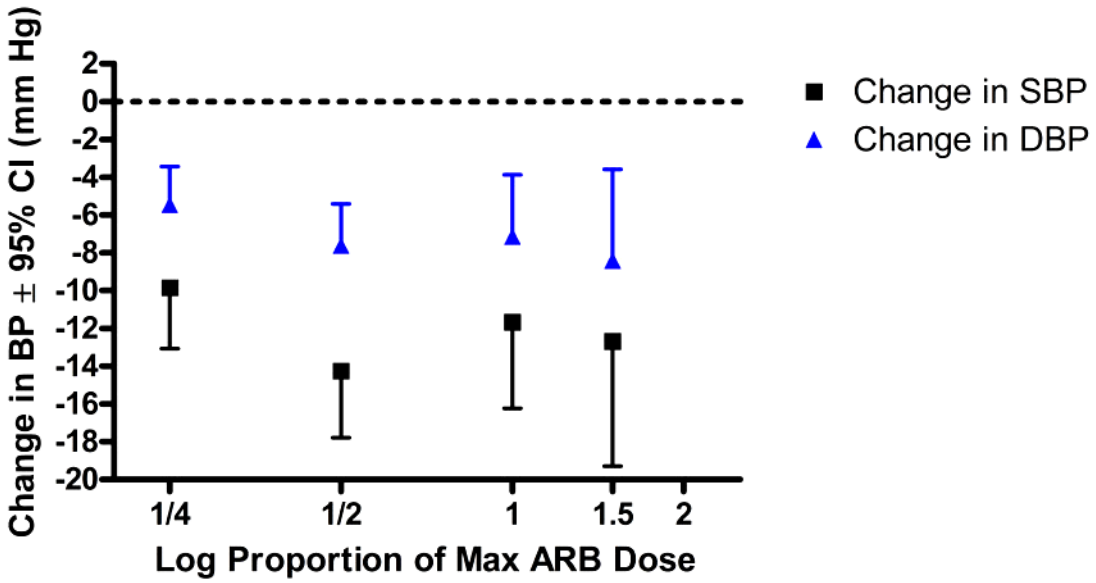
**Table 3.15: Standard deviations of BP at baseline versus endpoint in trials with DBP entry criteria**

| | | ARB | Placebo |
|---|---|---|---|
| Weighted mean SD of SBP | At baseline (SD) | 13.5 (2.2) | 13.2 (1.5) |
| | At endpoint (SD) | 16.9 (3.8) | 16.0 (2.2) |
| t-test | baseline vs. endpoint | $p = 0.03$ | $p = 0.03$ |
| Weighted mean SD of DBP | At baseline (SD) | 5.4 (1.6) | 4.9 (1.3) |
| | At endpoint (SD) | 8.1 (1.7) | 7.8 (1.6) |
| t-test | baseline vs. endpoint | $p = 0.002$ | $p < 0.006$ |

### 3.2.8 Dose-ranging peak blood pressure lowering efficacy

Four of the included trials reported the blood pressure lowering efficacy of ARBs at peak. The data were pooled for all trials by categorizing the individual doses as proportions of Max, encompassing a dose range of 1/4 to 1.5 Max (Figure 3.30).

**Figure 3.30: Log dose-response curve of peak BP lowering efficacy of ARBs according to proportions of Max**




All doses exhibited a statistically significant reduction in peak SBP and DBP compared with placebo. Indirect comparisons showed no statistically significant difference in the effect sizes between the doses. Thus, pooling the results of all the doses provides an estimate of the peak blood pressure lowering effect of ARBs, -11.58 (95% CI -13.52, -9.63) mm Hg for SBP and -6.53 (95% CI -7.78, -5.28) mm Hg for DBP.

### 3.2.9 Dose-ranging effect on pulse pressure

Pulse pressure was not reported as an outcome in any of the included trials. For each trial that reported both SBP and DBP outcomes, the change in pulse pressure from baseline was computed by subtracting the change in DBP from the change in SBP. An estimate of the placebo effect was calculated by pooling all trials that provided data. For ARBs, the available data were pooled and categorized according to proportions of the manufacturer's maximum recommended daily dose (Max). A weighted mean and associated standard deviation of the change in pulse pressure was calculated for each dose proportion (Table 3.16).

**Table 3.16: Change in pulse pressure according to proportions of Max**

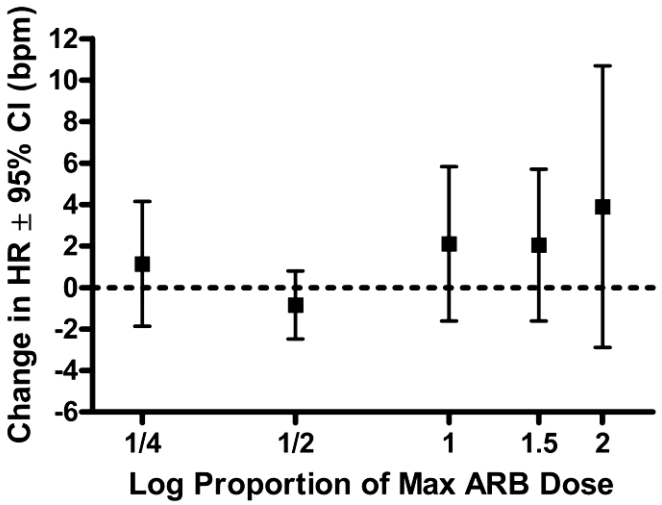
| | Proportion of recommended maximum dose (Max) | Number of studies | Weighted mean change from baseline in pulse pressure (95% CI) |
|---|---|---|---|
| ARB | 1/8 Max | 5 | -1.1 (-3.1, 0.9) |
| | 1/4 Max | 18 | -2.1 (-3.0, -1.1) |
| | 1/2 Max | 27 | -2.0 (-2.6, -1.4) |
| | Max | 13 | -2.5 (-3.6, -1.5) |
| | 1.5 Max | 5 | -1.1 (-2.2, 0.1) |
| | 2 Max | 3 | -2.9 (-6.2, 0.4) |
| | Max and above | 33 | -2.3 (-2.9, -1.7) |
| Placebo | | 34 | 1.1 (0.8, 1.5) |

There was a statistically significant 1 mm Hg increase in pulse pressure with placebo treatment. The 1/8 Max, 1.5 Max and 2 Max groups did not have a significant effect on change in pulse pressure, but this is likely due to the limited data available at these doses. However, at 1/4 Max, 1/2 Max and Max statistically significant reductions in pulse pressure were demonstrated. For ARBs at doses that achieved near maximal blood pressure lowering efficacy (Max and above), a statistically significant reduction of pulse pressure of 3.4 (95% CI 2.7, 4.1) as compared to placebo was present.

### 3.2.10 Dose-ranging effect on heart rate

Only five of the 46 included trials (11%) provided dose-related heart rate data [31,34,67,69,72]. All trials reported changes in heart rate at trough. Due to the lack of evidence for each ARB, the available data have been pooled and presented according to proportions of the manufacturers' maximum recommended daily dose (Max), ranging from 1/4 Max to 2 Max. Based on the limited data available, none of the doses showed a statistically significant change in heart rate compared with placebo (Figure 3.31).

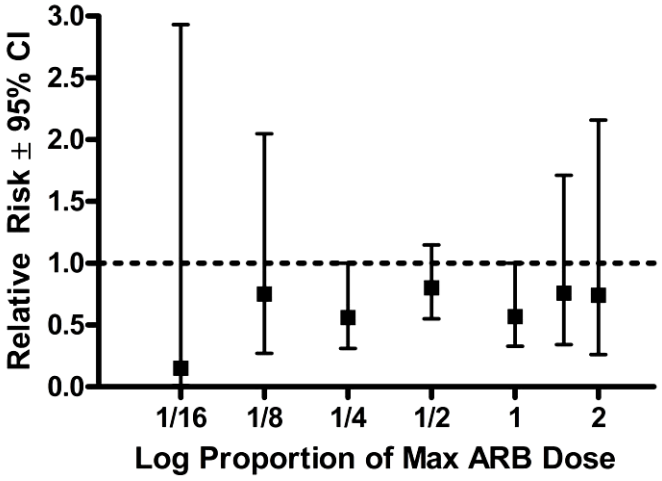
**Figure 3.31: Log dose-response curve assessing the effect of ARBs on heart rate**




### 3.2.11 Dose-ranging effect on withdrawals due to adverse effects

An analysis of withdrawals due to adverse effects (WDAE) during 3 to 12 weeks of treatment with ARBs was only reported in 26 (57%) of the included trials (Figure 3.32).

**Figure 3.32: Log dose-response curve assessing the effect of ARBs on withdrawals due to adverse effects**




There were insufficient data to evaluate the dose-related effect of the individual ARBs on withdrawals due to adverse effects. Thus, the tolerability data were pooled across ARBs according to proportions of Max to evaluate a possible dose-response

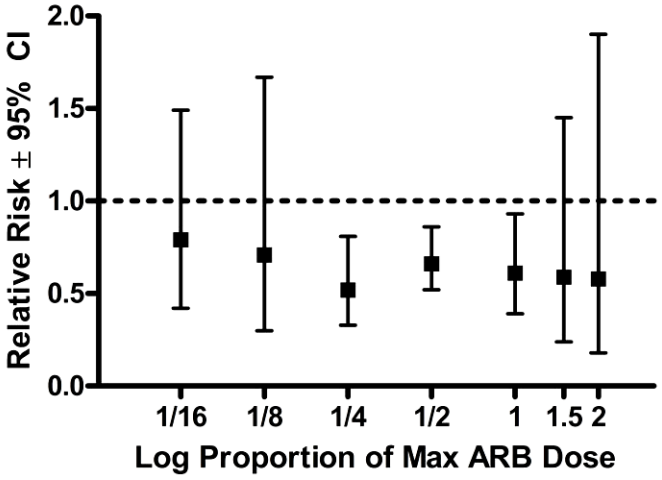
relationship.

There is no heterogeneity in any of the dosage groups and none of the doses showed a statistically significant difference from placebo. Based on the available evidence, there is no evidence of a dose-response relationship as an increase in the daily dose from 1/16 to 2 Max does not result in increased WDAE. In fact, when all doses are pooled, there is a statistically significant reduction in WDAE compared with placebo [RR 0.68 (95% CI 0.54, 0.87)]. Even the higher doses at which near maximal blood pressure lowering efficacy is achieved (Max dose and above), patients in the ARB group had a statistically significant reduction in WDAE [RR 0.64 (95% CI 0.43, 0.97)].

### 3.2.12 Dose-ranging effect on total withdrawals

Analysis of withdrawals for any reason during the double-blind treatment period was based on 13 (28%) of the 46 included trials. Compared with placebo, the 1/4 Max, 1/2 Max and Max dose groups showed a statistically significant reduction in total withdrawals (Figure 3.33).

**Figure 3.33: Log dose-response curve assessing the effect of ARBs on total withdrawals**




Only one trial provided data for each of the other dose groups, as reflected by the wide confidence intervals. Thus, due to limited power, these other doses showed no statistically significant difference from placebo. With all the doses pooled, there is a statistically significant relative risk of 0.63 (95% CI 0.53, 0.76), as compared to placebo.

## 3.3 Discussion

In this systematic review, 46 trials with a mean duration of 7 weeks met the pre-specified inclusion criteria and reported data on 13 451 participants (9028 treated with ARBs and 4423 treated placebo) with a mean age of 55 years, mean baseline blood pressure of 156/101 mm Hg and a mean pulse pressure of 55 mm Hg.

### 3.3.1 Is there a difference in the magnitude of BP lowering effect between individual drugs in the ARB class?

This review provides a reasonable amount of data to assess the trough blood pressure lowering efficacy of 9 different ARBs. When the different ARBs are compared, there is a similarity in their blood pressure lowering effects at trough. When the best estimate of the near maximal blood pressure lowering efficacy of these 9 drugs is compared, they range from -6/-3 mm Hg to -10/-7 mm Hg. For many of the drugs, there are insufficient data for a full range of doses. Therefore it remains possible that there could be differences between some of the drugs. However, the data are most consistent with the near maximum blood pressure lowering effect of each of the drugs being the same. It would require head-to-head trials of different ARBs at equivalent blood pressure lowering doses to assess whether or not there are differences in the blood pressure lowering efficacy between different drugs. This review provides useful dose-response information for estimating equivalent doses and thus designing trials to compare different ARBs.

### 3.3.2 What is the dose-related BP lowering effect of ARBs as a class?

Assuming that there are no major differences in blood pressure lowering efficacy between the drugs and the fact that the blood pressure lowering effects of the different ARBs were similar, this suggests that pooling of the data was appropriate for the 7 of 9 drugs that had manufacturers' recommended dosage information available. Data were pooled for the 7 ARBs by categorizing individual doses as proportions of the manufacturers' maximum recommended daily dose (Max). It is recognized that this approach has its limitations but it provided a non-arbitrary method for pooling the drugs. When this pooling was done, the ARBs, as a class, demonstrated a dose-response relationship. A dose of 1/16 Max achieved greater than 50% of the blood pressure

lowering effect of the maximum recommended dose. A dose of 1/8 or 1/4 Max achieved a blood pressure lowering effect that was 60 to 70% of the blood pressure lowering effect of the maximum recommended dose. A dose of 1/2 Max achieved a blood pressure lowering effect that was 80% of the maximum recommended dose.

Since the blood pressure lowering effect of doses above maximum recommended doses was not significantly different than that of the maximum recommended dose, it was felt to be reasonable to combine the effects of maximum recommended doses and higher to provide a reasonable estimate of the near maximal trough blood pressure lowering efficacy for the ARBs as a class of drugs. This was -9 mm Hg for SBP and -6 mm Hg for DBP. This was accompanied by an average reduction in trough pulse pressure of 3 mm Hg. This is quite a modest effect and is likely considerably less than most clinicians would estimate can be achieved with the drugs. However, this effect is at trough and is obtained after subtracting the placebo effect which averaged -2/-3 mm Hg. Furthermore, most doctors do not measure blood pressure in their patients at trough. In this review we had much less data for the effect of ARBs 1 to 12 hours after the dose. However, the available data suggest that the blood pressure lowering effect is modestly greater 1 to 12 hours after the dose than at trough, -11.6/-6.5 mm Hg.

### 3.3.3 For each ARB, do the manufacturer's dosage recommendations coincide with the findings of this review?

Assuming that the manufacturer's starting dose should approximate the lowest effective blood pressure lowering dose, table 3.17 shows that, based on this systematic review, the defined lowest effective dose for only 3 ARBs is in agreement with the manufacturer's recommended starting dose. For the other 4 ARBs, the defined lowest effective dose occurred at 1/4 of the recommended starting dose.

**Table 3.17: Comparison of manufacturers' dosage recommendations and findings of this review**

| ARB | Lowest effective dose (mg/day) | Manufacturer's recommended starting dose (mg/day) | Lowest dose with near maximal BP lowering (mg/day) | Manufacturer's recommended maximum dose (mg/day) |
|---|---|---|---|---|
| candesartan | 4 | 16 | 4 | 32 |
| eprosartan | 600 | 600 | 600 | 800 |
| irbesartan | 75 | 150 | 75 | 300 |

| ARB | Lowest effective dose (mg/day) | Manufacturer's recommended starting dose (mg/day) | Lowest dose with near maximal BP lowering (mg/day) | Manufacturer's recommended maximum dose (mg/day) |
|---|---|---|---|---|
| losartan | 50 | 50 | 50 | 100 |
| olmesartan | 20 | 20 | 20 | 40 |
| telmisartan | 20 | 80 | 40 | 80 |
| valsartan | 20 | 80 | 80 | 320 |

For 6 of the 7 ARBs the lowest dose with near maximal blood pressure lowering was achieved at 1/4 to 1/2 of the manufacturer's recommended maximum daily dose. Most of the blood pressure lowering with eprosartan was achieved at 75% of the recommended maximum dose. This may seem inconsistent with our decision to estimate the near maximal trough blood pressure lowering efficacy using the maximum recommended doses and above, but for each ARB there were insufficient data available at the higher doses to detect differences in blood pressure lowering between the lowest dose with near maximal blood pressure lowering efficacy and higher doses. However, when analyzed as a class (by categorizing the individual ARBs according to proportions of the manufacturer's maximum recommended dose), the lowest dose with near maximal blood pressure lowering efficacy was the maximum recommended dose.

### 3.3.4 What is the effect of ARBs on BP variability?

To determine the effect of ARBs on blood pressure variability the endpoint standard deviations of the ARB group were compared with the placebo group. This analysis showed that ARBs do not change blood pressure variability.

It appears that the blood pressure that was used as entry criteria into a trial affected blood pressure variability. Trials with systolic hypertension entry criteria had a lower baseline SBP variability than trials with entry criteria based on elevated DBP alone, or both elevated SBP and DBP. Likewise, in the trials with DBP entry criteria, the baseline variability of DBP was lower than at endpoint in both the ARB and placebo groups. This demonstrates that the entry criteria artificially lower the variability of the blood pressure measurements. Entry criteria artificially lower the magnitude of baseline variability because the normal distribution of the measurement is truncated and also because patients with DBP levels that are just below the cut-off for the trial are raised to

allow the patient to be enrolled into the trial. This enrollment bias is probably present in most blood pressure trials.

An unexpected finding was a lower baseline SBP standard deviation than at endpoint in both the ARB group and placebo group. This might be explained by the limited data as only 6 (13%) trials with DBP entry criteria reported endpoint SD. Furthermore, since placebo is highly unlikely to affect variability, it is more likely some artifact leading to decreased standard deviation at baseline rather than ARBs are causing an increase in blood pressure variability. Further investigation of head-to-head trials, crossover trials and 24-hour blood pressure monitoring studies will be needed to test this possibility.

The average estimates of the blood pressure variability in this review can be used as a means for evaluating the reliability of the data in trials. Based on the baseline variabilities in the treatment and placebo groups in trials with entry criteria based on elevated DBP alone, the average variability of SBP is 14.2 (SD 1.8) mm Hg. The average estimate of the variability of DBP cannot be determined from the reported values in our systematic review because 82% of the trials had DBP entry criteria. Instead, the average of the endpoint values in these trials, 8.1 (SD 1.7) mm Hg, is a reasonable estimate of the DBP variability. These average values of resting blood pressure variability include both inter- and intra-individual variability.

### 3.3.5 Is there evidence of a dose-response relationship for heart rate?

There is reasonable likelihood of selective reporting bias of resting heart rate since only about 10% of the trials reported data for this outcome. Based on the few trials for which data were available, ARBs did not have a significant effect on resting heart rate.

### 3.3.6 Is there evidence of a dose-response relationship for withdrawals due to adverse effects?

There were not enough data to construct a meaningful dose-response relationship for individual ARBs and when combined there still were insufficient data at higher doses to determine a dose-related effect on WDAE. The available data demonstrate that for all doses, ARBs resulted in a reduction in WDAE compared with placebo [RR 0.68 (95% CI

0.54, 0.87)]. However, only about half the trials reported the number of WDAE, so this finding has a high risk of selective reporting bias. A description of the type and severity of the adverse effects that led to premature withdrawal was rarely reported. Therefore, further information about the tolerability and safety of ARB treatment should be gathered from sources other than published reports of short-term efficacy trials, such as longer term randomized trials, non-randomized trials or post-marketing surveillance studies.

### 3.3.7 Limitations of the review

Many trials required imputation of the standard deviations of the blood pressure change because they did not report these values. However, our average estimates of the blood pressure lowering effect of these drugs were insensitive to the imputation strategy used.

One of the main limitations of this review is that not all the trials assessing the efficacy of ARBs have been published. We know that because many of the doses that have been approved by regulators are not included in this review. For example, eprosartan has been approved for a dose range of 600 to 800 mg in Canada and the USA. We only found data for the effect of 600 mg of eprosartan and we know that trials must have been completed and provided to the regulators for the 800 mg dose. Another indication that not all the efficacy trials have been published is the disparity between the manufacturers' recommendations and the results of our review (Table 3.17). For all ARB drugs, the manufacturers' maximum dose recommendations are higher than our evidence would suggest. It is likely that the manufacturers are basing their recommendations on more complete (i.e. published and unpublished) trial evidence.

The use of maximum recommended dose by the manufacturer as a way of trying to compare equivalent doses of the drugs is imperfect but served our purposes in this review. When this review is updated and we get more data on the dose-response for each drug, it may be possible to estimate the ED-50 of each of the available drugs and thus and thus use that criterion to combine the equieffective doses of the different ARBs.

### 3.3.8 What are the potential sources of bias?

#### 3.3.8.1 Sequence generation, allocation concealment

Details of the methods for generation of the sequence of allocations or allocation concealment were reported in only 2 of the 46 (4.4%) included studies. Nearly all the trial publications simply reported that the trial was "randomized" but did not provide any details about the randomization method or the method of allocation concealment. Given the fact that many investigators use the term "randomized" when it is not justified, such vague reporting is insufficient for determining whether or not the allocation sequence was properly randomized and adequately concealed. Authors should report their methods of sequence generation and allocation concealment clearly in order to assess the risk of bias in these studies.

#### 3.3.8.2 Blinding bias

Nearly all the trial publications simply reported that the trial was "double-blind" but did not provide any details about the blinding methods. Only 8 (17.4%) trials described the blinding method as "double dummy" or using a "matched" placebo. The potential for loss of blinding is unlikely because ARBs are not known to have any characteristic side effects. However, the success of blinding in patients or investigators was not assessed in any of the included trials.

#### 3.3.8.3 Attrition bias

It is unlikely that attrition bias would have had an impact on the systematic review since 90 to 100 percent of patients randomized to fixed-dose monotherapy in each trial completed the double-blind treatment period.

#### 3.3.8.4 Selective reporting bias

This would not affect the blood pressure measurements as these were the primary outcome of most of these trials. As mentioned above, there is a potential for selective reporting bias for heart rate and withdrawals due to adverse effects.

#### 3.3.8.5 Other potential sources of bias

A potential source of bias that we became aware of in working on this review is patient selection bias. One of the exclusion criteria reported in nearly all trials was participants with a known hypersensitivity to ACE inhibitors. This suggests that investigators have knowledge of each participant's prior experience with this older drug class with a similar mechanism of action. They thus could have potentially selected for patients who have responded favorably to ACE inhibitors or ARBs in terms of blood pressure lowering. If this was occurring to any degree, it may lead to an exaggerated blood pressure lowering response as compared to a totally unselected group of patients. However, it was not possible to prove selection bias as none of the included trials described the details of patient recruitment.

### 3.3.9 Publication bias

Yet another source of bias that may skew the results of systematic reviews is publication bias, which results from the selective publication of trials with positive results. This review was evaluated for the existence of publication bias since it only included and appraised published trial evidence. In the absence of bias, the funnel plot should resemble a symmetrical inverted funnel since the precision in the estimation of the true blood pressure lowering decreases as the study size decreases. Thus small studies will scatter more widely at the bottom of the graph [80]. The most common way to investigate whether a review is subject to publication bias is to examine for funnel plot asymmetry as smaller studies with null results may remain unpublished. Publication bias was detected for the ARB drug class as funnel plot asymmetry was observed. Examination of the funnel plots showed a paucity of small- to medium-sized studies with null results. Therefore, the magnitude of the blood pressure lowering efficacy of this class of drugs is likely an overestimate of the true effect.

A post-hoc tertile analysis was conducted for the class of ARB drugs to evaluate the extent of the impact publication bias had on the overall effect estimate of blood pressure lowering and, if possible, adjust for this bias. The studies were divided into three groups according to sample size in order to compare the mean effect estimates between the largest trials (highest tertile) and smallest trials (lowest tertile). The results of this

analysis corroborated the asymmetry observed in the funnel plots by demonstrating a statistically significantly greater estimate of the blood pressure lowering efficacy of ARBs in the smallest trials than in the largest trials (-9.9/-6.4 mm Hg vs -7.8/-5.1 mm Hg, respectively). In this case, the largest trials are probably providing the best estimate of the true blood pressure lowering effect of ARBs -8/5 mm Hg.

The results of the ARB review underscore the need for all studies, regardless of the findings, to be published and accessible for secondary analysis. Trial registration is recognized as one important way to improve transparency in research and knowledge sharing. In recent years, regulatory bodies around the world, led by the World Health Organization (WHO), have set standards for trial registration and reporting and are urging research institutions and companies to register all medical studies that test treatments on humans [81]. Initiatives such as the WHO's International Clinical Trials Registry Platform will help improve transparency and will allow the ability to identify trials that have been registered but not published.

## 3.4 Reviewers' conclusions

### 3.4.1 Implications for practice

#### 3.4.1.1 Specific findings of the review

1. The review provides data on the dose-related blood pressure lowering efficacy of 9 different ARBs at trough. The best estimate of the blood pressure lowering efficacy of these 9 drugs ranges from -6/-3 mm Hg to -10/-7 mm Hg. The data do not suggest that any one ARB is better or worse than any other at lowering blood pressure when used at maximal recommended doses.
2. A dose-response relationship for the blood pressure lowering effect of the ARBs was evident. A dose of 1/16 of the maximum recommended daily dose achieved greater than 50% of the blood pressure lowering effect of the maximum recommended dose. A dose of 1/8 or 1/4 of the maximum recommended daily achieved a blood pressure lowering effect that was 60 to 70% of the blood pressure lowering effect of the maximum recommended dose. A dose of 1/2 of the maximum recommended dose achieved a blood pressure lowering effect that was 80% of the maximum recommended dose.
3. ARB doses above the maximum recommended dose did not significantly lower blood pressure more than the maximum recommended dose.
4. Combining the effects of maximum recommended doses and higher gives an estimate of the resting trough blood pressure lowering efficacy for ARBs as a class of drugs of -9 mm Hg for SBP and -6 mm Hg for DBP.
5. Funnel plots and a tertile analysis provided evidence for publication bias leading to an overestimate of the true effect. Using a tertile analysis, the best estimate of the true blood pressure lowering effect was -8/-5 mm Hg.
6. ARBs reduced blood pressure measured 1 to 12 hours after the dose by about 12/7 mm Hg.
7. ARBs reduced trough pulse pressure by about 3 mm Hg.
8. ARBs did not significantly affect blood pressure variability or heart rate.
9. All doses of ARBs combined resulted in a reduction in WDAE compared with

placebo; however, this finding has a high risk of selective reporting bias and patient selection bias.

#### 3.4.1.2 Implications of these findings

This systematic review provides the best available published evidence about the dose-related blood pressure lowering efficacy of ARBs for the treatment of primary hypertension. These findings have the potential to change prescribing behavior and drug funding policies around the world. The evidence from this review suggests that there are no clinically meaningful differences between available ARBs for lowering blood pressure. Thus, substantial cost savings can be achieved by prescribing the least expensive ARB.

The major limitation of this review is that it is limited to published trials and it is evident that a lot of trials that manufacturers would have needed to gain marketing approval have not been published. Thus, in addition to the evidence of publication bias and the revised downward estimate of near maximal blood pressure lowering effect, there remains a further risk for publication bias based on manufacturers controlling what trials are published or not. It is also estimated that there is a high risk of patient selection bias that could have led to overestimation of the blood pressure lowering effect. For these reasons, the magnitude of blood pressure lowering found is this review is probably an overestimate of the true effect. This observation makes it even more surprising that the estimates of trough and peak blood pressure lowering effects of the ARBs are modest at best and lower than commonly believed can be achieved by this class of drugs. In addition, the review demonstrates that 60 to 70% of the blood pressure lowering effect occurs with recommended starting doses and that 80% is achieved with half the manufacturer's maximum recommended daily dose. If physicians prescribing ARBs were aware of this evidence, they would prescribe lower doses leading to substantial cost savings, and possibly leading to a reduction in dose-related adverse events.

The finding in this systematic review that there is a reduction in withdrawals due to adverse effects with an ARB as compared to placebo is surprising and unlikely to be true. This finding is limited by the short duration of these trials and is at high risk of selective publication bias, selective reporting bias and patient selection bias in these

trials. It is therefore unlikely that this reflects the true effect of ARBs on withdrawals due to adverse effects, which would need to be studied using different trial designs.

### 3.4.2 Implications for research

1. It is likely that not all trials completed on the blood pressure lowering effect of ARBs are published. It should be mandatory that all clinical trials be registered and the results of these trials be published in full detail.
2. Full dose-response data for doses within the recommended dose range and beyond the recommended dose range are needed to properly analyze the dose-response relationship for each ARB.
3. Trials should be designed to measure blood pressure data for peak effects as well as trough effects.
4. All trials should report withdrawals due to adverse effects and serious adverse events.

## 3.5 References


1. Heran BS, Wong MMY, Wright JM. Dose-related blood pressure lowering efficacy of angiotensin receptor blockers in the treatment of primary hypertension. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003822. DOI: 10.1002/14651858.CD003822.

2. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

3. Musini VM. A Systematic Review of the blood pressure lowering efficacy of thiazide and loop diuretics in the treatment of primary hypertension. M.Sc. Thesis, University of British Columbia 2000.

4. Heran BS, Jauca CD, Wright JM. Development of an optimal search strategy for finding trials demonstrating ACE inhibitor blood pressure lowering efficacy. 10th International Cochrane Colloquium, Stavanger, Norway 2002.

5. Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 6. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

6. Jadad AR, Moore RA, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trials 1996; 17:1-12.

7. Bucher HC, Guyatt GH, Griffith LE, Walker SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology 1997; 50(6):683-691.

8. Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003; 326:472-476.

9. Asmar R, Lacourciere Y. A new approach to assessing antihypertensive therapy: effect of treatment on pulse pressure. Journal of Hypertension 2000; 18(11):1683-90.

10. Lacourciere Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. American Journal of Hypertension 1999; 12(12 Pt 1-2):1181-7.

11. Asmar R. Effect of telmisartan on arterial distensibility and central blood pressure in patients with mild to moderate hypertension and Type 2 diabetes mellitus. Journal of the Renin-Angiotensin-Aldosterone System 2001; 2 Suppl 2:S8-11.

12. Association of Black Cardiologists (ABC) Candesartan Study Group. Evaluation of candesartan cilexetil in black patients with systemic hypertension: the ABC Trial. Heart Disease 2000; 2(6):392-9.

13. Bakris G, Sica D, Ram V, Fagan T, Vaitkus PT, Anders RJ, et al. A comparative trial of controlled-onset, extended-release verapamil, enalapril, and losartan on blood pressure and heart rate changes. American Journal of Hypertension 2002; 15(1 Pt 1):53-7.

14. Fagard R, Lijnen P, Pardaens K, Thijs L, Vinck W. A randomised, placebo-controlled, double-blind, crossover study of losartan and enalapril in patients with essential hypertension. Journal of Human Hypertension 2001; 15(3):161-7.

15. Fridman KU, Wysocki M, Friberg PR, Andersson OK. Candesartan cilexetil in hypertension: effects of six weeks' treatment on haemodynamics, baroreceptor sensitivity and the renin-angiotensin-aldosterone system. Blood Pressure 1999; 8(4):242-7.

16. Fridman K, Wysocki M, Friberg P, Andersson OK. Candesartan cilexetil and renal hemodynamics in hypertensive patients. American Journal of Hypertension 2000; 13(9):1045-8.

17. Hedner T, Himmelmann A. The efficacy and tolerance of one or two daily doses of eprosartan in essential hypertension. Journal of Hypertension 1999; 17(1):129-36.

18. Koh KK, Chung WJ, Ahn JY, Han SH, Kang WC, Seo YH, et al. Angiotensin II type 1 receptor blockers reduce tissue factor activity and plasminogen activator inhibitor type-1 antigen in hypertensive patients: a randomized, double-blind, placebo-controlled study. Atherosclerosis 2004; 177(1):155-60.

19. Koh KK, Han SH, Chung WJ, Ahn JY, Jin DK, Kim HS, et al. Comparison of effects of losartan, irbesartan, and candesartan on flow-mediated brachial artery dilation and on inflammatory and thrombolytic markers in patients with systemic hypertension. American Journal of Cardiology 2004; 93(11):1432-5.

20. Lacourciere Y, Lenis J, Orchard R, Lewanczuk R, Houde M, Pesant Y, et al. A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and amlodipine. Blood Pressure Monitoring 1998; 3(5):295-302.

21. Lacourciere Y. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. International Journal of Clinical Practice 1999; 53(2):99-103.

22. Marino MR, Langenbacher KM, Ford NF, Raymond RH, Manning J, Vesterqvist O, et al. Pharmacodynamics and pharmacokinetics of irbesartan in patients with mild to moderate hypertension. Journal of Cardiovascular Pharmacology & Therapeutics 1999; 4(2):67-75.

23. McInnes GT, O'Kane KP, Jonker J, Roth J. The efficacy and tolerability of candesartan cilexetil in an elderly hypertensive population. Journal of Human Hypertension 1997; 11 Suppl 2:S75-S80.

24. Neutel J, Weber M, Pool J, Smith D, Fitzsimmons S, Chiang YT, et al. Valsartan, a new angiotensin II antagonist: antihypertensive effects over 24 hours. Clinical Therapeutics 1997; 19(3):447-58.

25. Neutel JM, Bedigian MP. Efficacy of valsartan in patients aged > or =65 years with systolic hypertension. Clinical Therapeutics 2000; 22(8):961-9.

26. Petrov VV, Fagard RH, Lijnen PJ. T-lymphocyte and plasma angiotensin-converting enzyme activity during enalapril and losartan administration in humans. Journal of Cardiovascular Pharmacology 2001; 38(4):578-83.

27. Zanchetti A, Omboni S. Comparison of candesartan versus enalapril in essential hypertension. American Journal of Hypertension 2001; 14(2):129-34.

28. Zuschke CA, Keys I, Munger MA, Carr AA, Marinides GN, Flanagan TL, et al. Candesartan cilexetil: comparison of once-daily versus twice-daily administration for systemic hypertension. Clinical Therapeutics 1999; 21(3):464-74.

29. Andersson OK, Neldam S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. Blood Pressure 1998; 7(1):53-9.

30. Farsang C, Kawecka-Jaszcz K, Langan J, Maritz F, Zannad F. Antihypertensive effects and tolerability of candesartan cilexetil alone and in combination with amlodipine. Clinical Drug Investigation 2001; 21(1):17-23.

31. Fogari R, Zoppi A, Malamani G, Marasi G, Pesce RM, Banderali A, et al. Effects of four angiotensin II-receptor antagonists on fibrinolysis in postmenopausal women with hypertension. Current Therapeutic Research, Clinical & Experimental 2001; 62(1):68-78.

32. Meineke I, Feltkamp H, Hogemann A, Gundert-Remy U. Pharmacokinetics and pharmacodynamics of candesartan after administration of its pro-drug candesartan cilexetil in patients with mild to moderate essential hypertension--a population analysis. European Journal of Clinical Pharmacology 1997; 53(3-4):221-8.

33. Reif M, White WB, Fagan TC, Oparil S, Flanagan TL, Edwards DT, et al. Effects of candesartan cilexetil in patients with systemic hypertension. American Journal of Cardiology 1998; 82(8):961-5.

34. Gradman AH, Gray J, Maggiacomo F, Punzi H, White WB. Assessment of once-daily eprosartan, an angiotensin II antagonist, in patients with systemic hypertension. Clinical Therapeutics 1999; 21(3):442-53.

35. Oparil S. Eprosartan versus enalapril in hypertensive patients with angiotensin-converting enzyme inhibitor-induced cough. Current Therapeutic Research, Clinical & Experimental 1999; 60(1):1-4.

36. Punzi HA, Punzi CF. Once-daily eprosartan mesylate in the treatment of elderly patients with isolated systolic hypertension: data from a 13-week double-blind, placebo-controlled, parallel, multicenter study. Journal of Human Hypertension 2004; 18(9):655-61.

37. White WB, Anwar YA, Mansoor GA, Sica DA. Evaluation of the 24-hour blood pressure effects of eprosartan in patients with systemic hypertension. American Journal of Hypertension 2001; 14(12):1248-55.

38. Benetos A, Gautier S, Lafleche A, Topouchian J, Frangin G, Girerd X, et al. Blockade of angiotensin II type 1 receptors: effect on carotid and radial artery structure and function in hypertensive humans. Journal of Vascular Research 2000; 37(1):8-15.

39. Fogari R, Ambrosoli S, Corradi L, Degli EE, Mos L, Nami R, et al. 24-hour blood pressure control by once-daily administration of irbesartan assessed by ambulatory blood pressure monitoring. Journal of Hypertension 1997; 15(12 Pt 1):1511-8.

40. Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation 2005; 111(8):1012-8.

41. Guthrie R, Saini R, Herman T, Pleskow W, Sprecher D, Collins G. Efficacy and tolerability of irbesartan, an angiotensin II receptor antagonist, in primary hypertension. A double-blind, placebo-controlled, dose-titration study. Clinical Drug Investigation 1998; 15(3):217-27.

42. Kassler-Taub K, Littlejohn T, Elliott W, Ruddy T, Adler E. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild-to-moderate hypertension. American Journal of Hypertension 1998; 11(4 Pt 1):445-53.

43. Kochar M, Guthrie R, Triscari J, Kassler-Taub K, Reeves RA. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. American Journal of Hypertension 1999; 12(8 Pt 1):797-805.

44. Pool JL, Guthrie RM, Littlejohn TW, III, Raskin P, Shephard AM, Weber MA, et al. Dose-related antihypertensive effects of irbesartan in patients with mild-to-moderate hypertension. American Journal of Hypertension 1998; 11(4 Pt 1):462-70.

45. Cushman WC, Brady WE, Gazdick LP, Zeldin RK. The effect of a losartan-based treatment regimen on isolated systolic hypertension. Journal of Clinical Hypertension 2002; 4(2):101-7.

46. Flack JM, Saunders E, Gradman A, Kraus WE, Lester FM, Pratt JH, et al. Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension. Clinical Therapeutics 2001; 23(8):1193-208.

47. Flack JM, Oparil S, Pratt JH, Roniker B, Garthwaite S, Kleiman JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. Journal of the American College of Cardiology 2003; 41(7):1148-55.

48. Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snavely DB, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension 1995; 25(6):1345-50.

49. Hedner T, Oparil S, Rasmussen K, Rapelli A, Gatlin M, Kobi P, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. American Journal of Hypertension 1999; 12(4 Pt 1):414-7.

50. Ikeda LS, Harm SC, Arcuri KE, Goldberg AI, Sweet CS. Comparative antihypertensive effects of losartan 50 mg and losartan 50 mg titrated to 100 mg in patients with essential hypertension. Blood Pressure 1997; 6(1):35-43.

51. Mallion J, Siche J, Lacourciere Y. ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. Journal of Human Hypertension 1999; 13(10):657-64.

52. Schoenberger JA, Bauer J, Barden-Lane P, Brown R, Byyny R, Cohen J, et al. Losartan with hydrochlorothiazide in the treatment of hypertension. Journal of Hypertension - Supplement 1995; 13(1):S43-S47.

53. Weber MA, Byyny RL, Pratt JH, Faison EP, Snavely DB, Goldberg AI, et al. Blood pressure effects of the angiotensin II receptor blocker, losartan. Archives of Internal Medicine 1995; 155(4):405-11.

54. Byyny RL. Antihypertensive efficacy of the angiotensin II AT1-receptor antagonist losartan: results of a randomized, double-blind, placebo-controlled, parallel-group trial using 24-hour blood pressure monitoring. Blood Pressure 1996; Supplement. 2:71-7.

55. Byyny RL. Losartan potassium lowers blood pressure measured by ambulatory blood pressure monitoring. Journal of Hypertension - Supplement 1995; 13(1):S29-S33.

56. Weber MA, Neutel JM, Smith DH. Controlling blood pressure throughout the day: issues in testing a new anti-hypertensive agent. Journal of Human Hypertension 1995; 9 Suppl 5:S29-S35.

57. White WB, Sica DA, Calhoun D, Mansoor GA, Anders RJ. Preventing increases in early-morning blood pressure, heart rate, and the rate-pressure product with controlled onset extended release verapamil at bedtime versus enalapril, losartan, and placebo on arising. American Heart Journal 2002; 144(4):657-65.

58. Chrysant SG, Marbury TC, Robinson TD. Antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-to-moderate hypertension. Journal of Human Hypertension 2003; 17(6):425-32.

59. Chrysant SG, Weber MA, Wang AC, Hinman DJ. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. American Journal of Hypertension 2004; 17(3):252-9.

60. Neutel JM, Elliott WJ, Izzo JL, Chen CL, Masonson HN. Antihypertensive efficacy of olmesartan medoxomil, a new angiotensin II receptor antagonist, as assessed by ambulatory blood pressure measurements. Journal of Clinical Hypertension 2002; 4(5):325-31.

61. Feldman R, Chattman MS, Lonigro A, Sievers II RJ. Tasosartan in patients with essential hypertension: A randomized, double-blind dose-titration study. Advances in Therapy 1997; 14(5):290-303.

62. Lacourciere Y, Pool JL, Svetkey L, Gradman AH, Larochelle P, de Champlain J, et al. A randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of four doses of tasosartan in patients with essential hypertension. American Journal of Hypertension 1998; 11(4 Pt 1):454-61.

63. Neutel JM, Buckalew V, Chrysant SG, Mroczek WJ, Ruff DA, Weber M. Efficacy and tolerability of tasosartan, a novel angiotensin II receptor blocker: results from a 10-week, double-blind, placebo-controlled, dose-titration study. American Heart Journal 1999; 137(1):118-25.

64. Manolis AJ, Reid JL, de Zeeuw D, Murphy MB, Seewaldt-Becker E, Koster J, et al. Angiotensin II receptor antagonist telmisartan in isolated systolic hypertension (ARAMIS) study: efficacy and safety of telmisartan 20, 40 or 80 mg versus hydrochlorothiazide 12.5 mg or placebo. Journal of Hypertension 2004; 22(5):1033-7.

65. McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. Clinical Therapeutics 2001; 23(6):833-50.

66. McGill JB, Reilly PA. Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension. Clinical Cardiology 2001; 24(1):66-72.

67. Neutel JM, Smith DHG. Dose response and antihypertensive efficacy of the AT1 receptor antagonist telmisartan in patients with mild to moderate hypertension. Advances in Therapy 1998; 15(4):206-17.

68. Smith DHG, Neutel JM, Morgenstern P. Once-daily telmisartan compared with enalapril in the treatment of hypertension. Advances in Therapy 1998; 15(4):229-40.

69. Smith DH, Matzek KM, Kempthorne-Rawson J. Dose response and safety of telmisartan in patients with mild to moderate hypertension. Journal of Clinical Pharmacology 2000; 40(12 Pt 1):1380-90.

70. Benz JR, Black HR, Graff A, Reed A, Fitzsimmons S, Shi Y. Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy. Journal of Human Hypertension 1998; 12(12):861-6.

71. Black HR, Graff A, Shute D, Stoltz R, Ruff D, Levine J, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. Journal of Human Hypertension 1997; 11(8):483-9.

72. Hanefeld M, Abletshauser C. Effect of the angiotensin II receptor antagonist valsartan on lipid profile and glucose metabolism in patients with hypertension. Journal of International Medical Research 2001; 29(4):270-9.

73. Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, Oddou-Stock P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. Journal of Hypertension 1996; 14(9):1147-51.

74. Klingbeil AU, John S, Schneider MP, Jacobi J, Weidinger G, Schmieder RE, et al. AT1-receptor blockade improves augmentation index: a double-blind, randomized, controlled study. Journal of Hypertension 2002; 20(12):2423-8.

75. Klingbeil AU, John S, Schneider MP, Jacobi J, Handrock R, Schmieder RE, et al. Effect of AT1 receptor blockade on endothelial function in essential hypertension. American Journal of Hypertension 2003; 16(2):123-8.

76. Oparil S, Dyke S, Harris F, Kief J, James D, Hester A, et al. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. Clinical Therapeutics 1996; 18(5):797-810.

77. Pool JL, Glazer R, Chiang YT, Gatlin M. Dose-response efficacy of valsartan, a new angiotensin II receptor blocker. Journal of Human Hypertension 1999; 13(4):275-81.

78. Patterson D, Webster J, McInnes G, Brady A, MacDonald T, Patterson D, et al. The effects of KT3-671, a new angiotensin II (AT 1) receptor blocker in mild to moderate hypertension. British Journal of Clinical Pharmacology 2003; 56(5):513-9.

79. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2007 [updated 2006 Feb 27; cited 2007 Dec 1]. Micardis [product monograph]. Available from: www.e-cps.ca. Also available in paper copy from the publisher.

80. Deeks JJ, Higgins, JPT, Altman DG, editors. Analysing and presenting results. In: Higgins, JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 8. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

81. World Health Organization. International Clinial Trials Registry Platform (ICTRP). [Online] 2007 [cited 2007 November 17]. Available from: URL: http://www.who.int/ictrp/en/

# 4 DISCUSSION

The systematic reviews of the blood pressure lowering efficacy of ACE inhibitors and ARBs were based on randomized, placebo-controlled trials ranging from 3 to 12 weeks in duration. We have used these two reviews to investigate the dose-related effects of ACE inhibitors and ARBs on systolic and diastolic blood pressure, heart rate and withdrawals due to adverse effects in patients with primary elevations in blood pressure. Similar trial inclusion criteria and methods of analysis were used deliberately to be able to compare the results of these two reviews. An important goal of this research was to determine if there is a difference in the magnitude of blood pressure lowering between the two drug classes that inhibit the RAAS by different mechanisms. The discussion and conclusions that follow are based solely on the published trial evidence that met the inclusion criteria of the two systematic reviews.

## 4.1 How does this evidence contribute to current clinical practice?

### 4.1.1 Blood pressure lowering efficacy

Because of the high prevalence of hypertension and the fact that most patients who are started on drug therapy will take the drug for the rest of their life, the choice of treatment for the management of elevated blood pressure has enormous consequences for the individual patient and the health care system. It is imperative that choosing a drug incorporates evidence for reducing morbidity and mortality, efficacy in lowering blood pressure, tolerability and cost in the decision.

Mortality and morbidity are the most important considerations in terms of the choice, but these systematic reviews were not designed to provide any information about these outcomes. These reviews provide evidence predominantly for the blood pressure lowering efficacy and to a lesser degree for the tolerability of two classes of drugs, the ACE inhibitors and ARBs. These drugs are widely prescribed for hypertension and therefore it is essential to know whether or not there are differences between the classes for these two outcomes. It is also important to know how these classes compare with other classes of blood pressure lowering drugs.

The placebo response was highly variable but the mean effect was similar in both reviews. The weighted mean changes in SBP and DBP in placebo groups across all trials

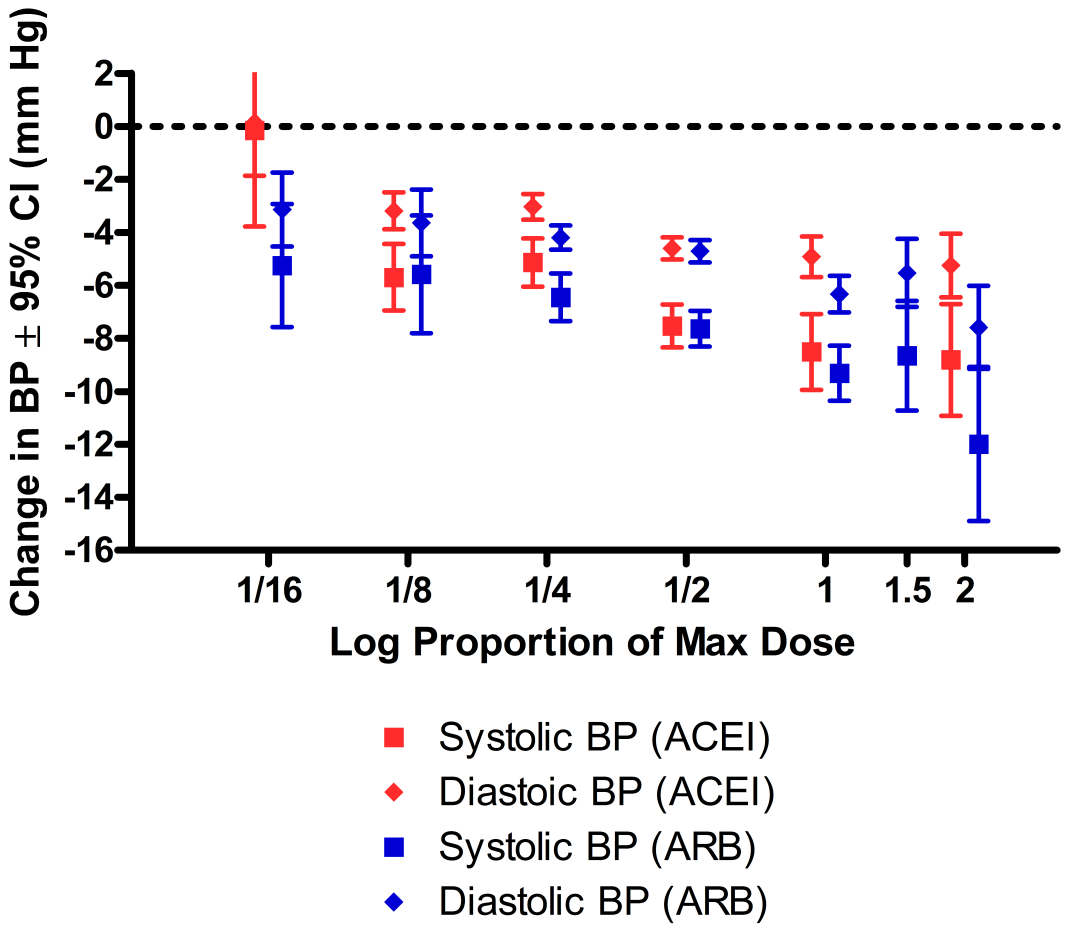
were -3.2 (range -14.7 to 3.7) mm Hg and -3.7 (range -10.1 to 3.0) mm Hg, respectively, in the ACE inhibitor review. In the ARB review, the placebo effect was -2.3 (range -13.4 to 3.2) mm Hg for SBP and -3.3 (range -7.7 to -0.4) mm Hg for DBP. Therefore, it was important to subtract this effect for each trial in order to determine the true blood pressure lowering effect of the individual ACE inhibitors and ARBs.

The two systematic reviews show that the blood pressure lowering effect of ACE inhibitors, as assessed by the best estimate of the near maximal trough effect, is slightly less than the same estimate for ARBs. If this was a real difference, it could have significant consequences because on a population level even a difference as small as 1 mm Hg could have important implications. However, the systematic review of ARBs showed evidence of publication bias and the estimate of blood pressure lowering by the ARBs is most likely artificially exaggerated. This is further discussed under publication bias below and when the correction for publication bias is applied the best estimate for the trough blood pressure lowering efficacy of ARBs is the same as for ACE inhibitors.

This similarity in efficacy is also confirmed in the few trials that reported near maximal peak effect for ACE inhibitors and ARBs. The estimate was -12 mm Hg for SBP and -7 mm Hg for DBP for both classes of drugs.

A difference between the two reviews that deserves discussion is that the shape of the dose-response curves appears to be different (Figure 4.1).

**Figure 4.1: Comparison of the BP lowering effect of ACE inhibitors and ARBs according to proportions of the manufacturer's recommended maximum daily dose**




The curve for the ACE inhibitors looks most like one would expect for a drug with the effect reaching a plateau at about one-half the maximum recommended dose. The curve for the ARBs is less characteristic with no doses showing no effect and a lack of a sigmoid shape. However, rather than representing a true difference between the two classes, we think it is more likely due to the limitations of the methods and the fact that the use of the manufacturer's maximum recommended dose is probably not equivalent between each of the drugs and not equivalent between the two reviews. It may be possible to correct this limitation in the future by using a better method for defining the dose-response relationship for each drug. Even given the limitations of the methods used, there are more similarities between the two classes of drugs than differences.

It will also be important to compare the blood pressure lowering efficacy of these two classes of drugs with other blood pressure lowering agents, such as thiazides, calcium channel blockers and beta blockers. At the present time that is not possible as those reviews are not published [1,2,3].

### 4.1.2 Pulse pressure, blood pressure variability and heart rate

Although pulse pressure is an important risk factor for cardiovascular disease, it was not reported as an outcome in any of the included studies. The weighted mean change in pulse pressure was therefore calculated from trials reporting trough changes in SBP and DBP. Compared with placebo, both ACE inhibitors and ARBs significantly reduced pulse pressure at doses achieving near maximal blood pressure lowering effect by 3.5 (95% CI 2.7, 4.3) and 3.4 (95% CI 2.7, 4.1) mm Hg, respectively. There is no statistically significant difference between the two drug classes for this outcome.

Using the same methods to estimate the effect of placebo on pulse pressure, placebo was found to statistically significantly increase pulse pressure from baseline by 1 mm Hg in both reviews. This was unexpected since it is hard to explain how a placebo would lead to an increase in pulse pressure. It is therefore more likely due to an artifact of the trial design used. Both reviews showed a greater placebo-induced reduction from baseline in DBP (3.3-3.7%) than in SBP (1.5-2.0%) leading to the increase in pulse pressure. It is important to note that nearly all the trials that were used to calculate pulse pressure had diastolic blood pressure entry criteria. That fact thus likely led to a greater regression toward the mean for DBP than for SBP, thus explaining the small increase in pulse pressure observed.

To determine the effect of ACE inhibitors and ARBs on blood pressure variability, the endpoint standard deviations of the two drug classes were compared with placebo. This analysis showed that ACE inhibitors and ARBs do not affect blood pressure variability since there was no statistically significant difference between either ACE inhibitors or ARBs and placebo for SBP or DBP. Compared with placebo, the variability of the change in systolic and diastolic blood pressure is not statistically significantly altered by the treatment with ACE inhibitors or ARBs. Therefore, it can be concluded that neither ACE inhibitors nor ARBs have an effect on blood pressure

variability. This is an important observation as it is desirable to find drug classes that reduce blood pressure variability in addition to reducing blood pressure magnitude.

There were few trials to adequately assess the heart rate effect of individual ACE inhibitors and ARBs, so the data was pooled for all trials that reported this outcome for each review. Based on this limited evidence, ACE inhibitors and ARBs had no significant effect on heart rate. However, since most trials did not report this outcome, this result is at risk of selective reporting bias.

### 4.1.3 Tolerability

The other outcome that can be compared in these two reviews is short-term tolerability. The best outcome to measure this is withdrawals due to adverse effects. This outcome was only reported in slightly over half of the trials so it is also likely subject to selective outcome reporting bias. It is possible that in trials which showed an increase in withdrawals due to adverse effects with the drugs as compared to placebo this outcome was selectively not reported. We also suspect that a large number of trials that have been completed have not been published. Therefore, we cannot conclude that there is a difference in tolerability between these two classes of drugs based on these two reviews. Long-term tolerability would be best assessed by head-to-head long-term trials designed to measure that outcome.

## 4.2 How do the effects of ACE inhibitors and ARBs on BP and tolerability, as determined by our reviews, compare with their theoretical mechanisms of action?

As discussed in the introductory chapter, each drug class has theoretical benefits in terms of blood pressure lowering efficacy as well as tolerability that are unique and specific to its mechanism of action. ACE inhibitors and ARBs reduce blood pressure by inhibiting the RAAS, a physiologic system that plays an important role in blood pressure regulation. The critical mediator in this system is AII and ACE inhibitors and ARBs were developed to treat hypertension by blocking the biological effects of this hormone. The mechanism by which this is achieved differs between the two drug classes.

ACE inhibitors block the formation of AII by competitively inhibiting ACE, an enzyme that catalyzes the formation of AII. ACE inhibitors do not have an impact on

other enzymes that are also known to catalyze AII formation. For this reason, ACE inhibitors may not be totally effective in inhibiting the formation of AII and thus its ability to elevate blood pressure. However, ACE inhibitors may also reduce blood pressure to a certain extent by inhibiting the degradation of the vasodilator bradykinin and other kinins. This mechanism is unique to the ACE inhibitor drug class but it is not known if this results in a clinically significant reduction in blood pressure. What is known is that accumulation of bradykinin and other kinins in the lungs probably results in a persistent refractory cough in some patients treated with these drugs. Accumulation of kinins is also believed to be the cause of angioedema, another side effect of ACE inhibitors.

ARBs inhibit the binding of AII to the AT1 receptor, which is believed to mediate AII's effect on blood pressure. They do not inhibit the breakdown of bradykinin and other kinins and thus are not associated with cough or angioedema. ARBs have been purported to block the RAAS more effectively than ACE inhibitors because the blockade is independent of the pathway for AII formation.

Despite the theoretical mechanisms whereby one class of drugs might be superior to the other in terms of blood pressure lowering efficacy, the results of the two systematic reviews do not demonstrate any difference between ACE inhibitors and ARBs in blood pressure lowering efficacy. This suggests that the theoretical mechanisms whereby they would have a different effect on blood pressure are not relevant to the clinical effects.

### 4.3 What methodological limitations were evident during the course of these systematic reviews?

A number of methodological issues were encountered while conducting the systematic reviews. Since both reviews were practically identical in terms of the methods and procedures used to search for relevant trials, extract the appropriate data and perform the data analyses, the problems that arose were the same for both systematic reviews.

Developing and implementing the search strategy was a time-consuming and inefficient process, given the high sensitivity and low specificity of searches using Medline and EMBASE. Since its introduction in 1994, the search strategy recommended by the Cochrane Collaboration, known as the Cochrane highly sensitive search strategy,

has become a standard for the retrieval of controlled trials from Medline using OVID. A modified and expanded search strategy was developed based on the Cochrane highly sensitive search strategy in an effort to identify studies that were missed by the standard Cochrane search strategy. The new strategy mildly increased the sensitivity but reduced the specificity. The modified search strategy identified five additional trials that met the inclusion criteria for the systematic review of ACE inhibitors, but only two studies had data available. No additional studies were identified for the systemic review of ARBs. All five trials, which were published in the early 1980's, were missed by the standard search strategy because they were not adequately indexed in Medline.

A shortcoming of the OVID search interface is the inability to utilize a suffix as a search term. Both ACE inhibitors ("-pril") and ARBs ("-sartan") have suffixes that are unique to these classes of drugs, so incorporating a suffix as a search term would have been beneficial in identifying relevant trials for both systematic reviews.

Searching CENTRAL, the Cochrane Library's specialized register of controlled trials of health care interventions provided high sensitivity and improved specificity for the identification of relevant trials. CENTRAL identified 136/138 (99%) of the trials included in both systematic reviews. Therefore, CENTRAL may be a time-saving alternative to searching other comprehensive electronic databases for pertinent trials in this type of review.

A systematic review is largely dependent on the quality of reporting in the published trials. When reporting in the publications was incomplete attempts were made to obtain the data or other pertinent information from the contact authors but rarely with any success. Of the authors who responded, only a small proportion clarified methodological details and no authors actually provided the additional quantitative data requested.

The risk of error while extracting data from the trial reports was minimized by having this step performed by two independent reviewers. A majority of trial reports provided data in tables but some publications only provided data in the text or in graphs. If the same data were provided in a graph as well as in the text, then the latter source took precedence since data extraction from a graph is not only potentially less accurate but also time-consuming. Twenty eight of the 92 (30%) included ACE inhibitor trials and 15

of the 46 (33%) included ARB trials provided data in graphs only. These trials should have also made the data available in tabular format as well.

The most frequently unreported data was the standard deviation of blood pressure change. Only 38 of the 92 (41%) included trials and 30 of the 46 (62%) included trials reported this value in the systematic reviews of ACE inhibitors and ARBs, respectively, and thus had to be imputed. A few trials that reported the standard deviation of blood pressure change also had to have this value imputed because the reported values were either too low or too high. Since the Review Manager software uses the standard deviation of change together with the sample size to compute the weight given to each study – i.e. studies with smaller standard deviations are given relatively higher weight while studies with larger standard deviations are given relatively lower weight – it is imperative that this value is accurately reported. In some of the trials where the standard deviations were too low, the authors erroneously reported a standard error as a standard deviation (sometimes the terminology was used inconsistently in the trial report) – so the correct values were computed and then entered in Review Manager. When trials reported standard deviations of blood pressure change that were more than 3 standard deviations away from the overall weighted mean, the values were discarded and replaced with imputed values.

## 4.4 What are the potential sources of bias in these systematic reviews?

### 4.4.1 Sequence generation bias, allocation concealment bias

Details of the methods for generation of the sequence allocation or allocation concealment were reported in only 5 of the 92 (5.4%) trials included in the ACE inhibitor review and 2 of the 46 (4.4%) trials included in the ARB review. Instead, the publications of nearly all the included trials in both reviews simply reported that the trial was "randomized". Such vague reporting is insufficient for evaluating whether the trial was properly randomized and adequately concealed given the fact that many investigators use the term “randomized” when it is not justified. Authors should therefore report their methods of sequence generation and allocation concealment clearly. Despite the poor reporting of these details in this review, it assumed that these steps were adequately

carried out in most cases and that there is an overall low risk of bias due to these methods.

### 4.4.2 Blinding bias

There is a potential of loss of blinding in all antihypertensive trials due to the fact that the investigators and patients know the blood pressure measurements. In addition, there was a potential for loss of blinding in the trials studying ACE inhibitors since these drugs have a well-known side effect that is unique to this class of drugs, a refractory cough. However, none of the included studies reported a significantly higher rate of cough or withdrawals due to cough over placebo in patients treated with ACE inhibitors.

The potential for loss of blinding with ARBs is less likely because this class of drugs is not known to have any characteristic side effects. The success of blinding in patients or investigators was not assessed in any of the trials included in both reviews. It is assumed that blinding was maintained is most of these trials and that the risk of bias due to this criterion is low.

### 4.4.3 Attrition bias

There is judged to be a low risk of attrition bias in these reviews as 89 to 100 percent of patients randomized to fixed-dose monotherapy with an ACE inhibitor or ARB in each trial completed the full follow-up in these relatively short-term trials.

### 4.4.4 Selective reporting bias

This is judged to have a low risk of causing bias in the blood pressure measurements in this review as blood pressure was the primary outcome of most of the trials included in the ACE inhibitor and ARB reviews. As mentioned above, we have judged that there is a high risk of selective reporting bias for heart rate and withdrawals due to adverse effects in these reviews.

### 4.4.5 Other potential sources of bias

Another potential source of bias that we became aware of in working on these reviews is specific to this type of review and outcome, patient selection bias. One of the exclusion criteria reported in nearly all trials was participants with a known

hypersensitivity to ACE inhibitors. Although hypersensitivity to an ACE inhibitor may not have any connection to cough, it suggests that investigators have knowledge of each participant's prior experience with this drug class and thus may have selected patients who have responded favorably to ACE inhibitors or ARBs in terms of blood pressure lowering or have selected patients who have previously been found to tolerate ACE inhibitors or ARBs. It was not possible to identify to what degree this type of patient selection bias was occurring as none of the included trials described this particular detail of patient recruitment. Despite this, we judge that there is a high risk of bias in this review due to this criterion.

One can hypothesize that those patients who are known responders in previous trials tend to be recruited to participate in subsequent trials, so more recent trials may show a greater magnitude of blood pressure lowering efficacy. This hypothesis was tested in both systematic reviews by performing a post-hoc tertile analysis according to the year of trial publication. The trials were divided into three groups and the oldest group of trials was compared with the group of most recent trials for mean blood pressure lowering efficacy. For both ACE inhibitors and ARBs, this analysis did not show a statistically significant difference in blood pressure lowering between the oldest and most recent group of trials. Therefore, this test does not confirm this type of bias, however; it does not rule out the possibility of an equal amount of patient selection bias occurring during both older and newer trials.

### 4.4.6 Publication bias

Since the reviews of ACE inhibitors and ARBs only included and appraised published trial evidence, both systematic reviews were evaluated for the existence of publication bias, which results from the selective publication of trials with positive results. Examination of the funnel plots generated from the results of the ACE inhibitor review did not show any signs of asymmetry due to unpublished smaller studies with null results. A post-hoc tertile analysis demonstrated no difference in the mean blood pressure lowering effect estimates between the largest trials and smallest trials, thus corroborating the symmetry observed in the funnel plots. Based on this information, it is reasonable to

conclude that publication bias did not impact the estimate of the blood pressure lowering effect size of ACE inhibitors.

Publication bias was detected for the ARB drug class; funnel plot asymmetry was observed. Examination of the funnel plots showed a paucity of small- to medium-sized studies with null results. The results of a post-hoc tertile analysis corroborated the funnel plot asymmetry by demonstrating a statistically significantly greater estimate of the blood pressure lowering efficacy of ARBs in the smallest trials as compared to the largest trials. In this case, the largest trials provide the best estimate of the true blood pressure lowering effect of ARBs and this leads to a 1 mm Hg reduction in the estimate for both systolic and diastolic blood pressure.

### 4.4.7 Overall comparison of the two classes of drugs

These two reviews provide reasonably good evidence that ACE inhibitors and ARBs reduce blood pressure and have similar effects on the other measured cardiovascular outcomes. The data on tolerability are weaker, but tolerability of the two classes was also similar in the short-term trials assessed here. There is also no convincing evidence of a morbidity and mortality benefit of one class of drugs over the other from other data. Therefore, the choice of drug between the two classes and within each class should be based on which drug is the least expensive.

### 4.4.8 Future considerations

The results of these reviews underscore the need for all studies, regardless of the findings, to be published and accessible for secondary analysis. In order to improve transparency in research and knowledge sharing, initiatives such as the World Health Organization's International Clinical Trials Registry Platform [4] have set standards for trial registration and reporting of all medical studies that test treatments on humans. These initiatives will help improve transparency and reduce the risk of publication bias skewing the results of future systematic reviews.

## 4.5 Implications for practice

### 4.5.1 Specific findings of these reviews

1. The best estimate of the near maximal trough blood pressure lowering efficacy of ACE inhibitor class of drugs and of the ARB class of drugs after adjusting for publication bias is -8 mm Hg for SBP and -5 mm Hg for DBP.
2. ACE inhibitors and ARBs reduced peak blood pressure to a similar extent. The best estimate of the peak blood pressure lowering efficacy of ACE inhibitors and ARBs is -12 mm Hg for SBP and -7 mm Hg for DBP.
3. ACE inhibitors and ARBs did not significantly affect blood pressure variability.
4. ACE inhibitors and ARBs did not significantly affect heart rate.
5. There is insufficient evidence to demonstrate a difference in short-term tolerability between ACE inhibitors and ARBs.

### 4.5.2 Implications of these findings

These two systematic reviews provide the best available published evidence about the dose-related blood pressure lowering efficacy of ACE inhibitors and ARBs for the treatment of primary hypertension. The results of these systematic reviews have the potential to change prescribing behavior and drug funding policy around the world. The evidence is compelling that there are no clinically meaningful differences between ACE inhibitors and ARBs in their ability to lower blood pressure. However, there is a considerable difference in cost, with ARBs being on average more expensive than ACE inhibitors. Furthermore, there are presently eight ACE inhibitors (and no ARBs) that are available in generic form around the world. Therefore, when choosing a drug inhibiting the renin angiotensin aldosterone system to lower blood pressure, the least costly generic ACE inhibitor should be the first choice. Prescribing of ARBs would thus be limited to patients proven to not tolerate ACE inhibitors due to, for example, angioedema or refractory intolerable cough. Using this rational approach, substantial savings to both drug funding bodies and to patients could be achieved as, at the present time, most physicians and funding agencies do not adhere to this framework to guide clinical and policy decision making. Due to a high risk of selective reporting bias and patient

selection bias, a reliable comparison of ACE inhibitors and ARBs for tolerability cannot be made. The reasons for this are explained in the preceding chapters.

In addition to the clinical implications these two reviews have considerable research implications. These reviews provide substantial efficacy evidence that both drug classes lower blood pressure to a similar degree despite having different mechanisms of action. Thus, any theoretical benefits attributed to the mechanism of action of each drug class are not manifest in terms of blood pressure lowering. This is important as many physicians choose between ACE inhibitors and ARBs based on theoretical benefits demonstrated in experimental models. Likewise, any theoretical differences within the ACE inhibitor or ARB class are not manifest in terms of the blood pressure lowering efficacy demonstrated here.

### 4.6 Research implications

1. The Cochrane Central Register of Controlled Trials (CENTRAL) provides high sensitivity and specificity for trials in the field of blood pressure lowering in hypertension, identifying 99% of the trials included in both systematic reviews. CENTRAL could be a time-saving alternative to searching other comprehensive electronic databases for studies.
2. Since a systematic review is a secondary analysis of the data from primary research (i.e. clinical trials), it is imperative that the quality of reporting be improved. Complete information on the following parameters must be provided in all trials.
   2.1. Methodological details; specifically the method of randomization of double blinding and allocation concealment.
   2.2. Baseline demographics regarding the age, sex, and race, plus data on what patients have been previously treated with the tested class or related class and their response.
   2.3. The number of patients who completed the trial, those who discontinued prematurely for all randomized groups, and the reasons for dropping out.
   2.4. Blood pressure parameters for all randomized groups; baseline, endpoint and the mean change from baseline, along with standard deviation values for each parameter in tables not figures.

2.5. The number of serious adverse events, deaths, withdrawals due to adverse effects and the number of adverse effects for all randomized groups.

3. All trials must be registered and the results of these trials be published in full detail.
4. Selective reporting bias and patient selection bias may have influenced the adverse effect results collected for the two systematic reviews. A systematic review of the adverse effects of ACE inhibitors and ARBs in treatment naïve patients, or those patients who have never been treated before with ACE inhibitors or ARBs, needs to be performed to adequately evaluate the true tolerability profile of these drugs.
5. More trials on a wider range of doses for each drug are needed to establish a complete dose-response relationship.
6. A separate systematic review of crossover trials of ACE inhibitors and ARBs for the treatment of primary hypertension would provide complementary evidence to these two systematic reviews about the blood pressure lowering efficacy of ACE inhibitors and ARBs.
7. Three additional systematic reviews can be conducted to answer other related questions. Most of the trials to answer these questions have already been collected in the list of included or excluded trials for the above reviews.

    7.1. What is the effect of ACE inhibitors as compared to ARBs in patients with elevated blood pressures on office blood pressure from head-to-head trials? This review would more directly answer the question of whether the blood pressure lowering effect of ACE inhibitors is different from that of ARBs.

    7.2. What is the effect of combination therapy with an ACE inhibitor and ARB at near maximal effective doses as compared to monotherapy with an ACE inhibitor and with an ARB in patients with elevated blood pressure on office systolic and diastolic blood pressure from head-to-head trials? This review would answer the question of whether or not the blood pressure lowering effect of combination therapy is different from that of ACE inhibitors and ARBs alone.

    7.3. What is the effect of ACE inhibitors and ARBs as compared to placebo on waking and sleeping blood pressure based on 24-hour ambulatory blood pressure trials? This review would provide an estimate of the blood pressure lowering efficacy over the full 24-hour dosing period.

7.4. What is the blood pressure lowering efficacy of ACE inhibitors and ARBs beyond 12 weeks of treatment? This review would answer the question of whether the blood pressure lowering effects of ACE inhibitors and ARBs is sustained over a longer period of time.

## 4.7 References


1. Musini VM, Wright JM, Bassett KL, Jauca CD. Blood pressure lowering efficacy of thiazide diuretics for primary hypertension. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003824. DOI: 10.1002/14651858.CD003824.

2. Wong MMY, Heran BS, Wright JM. Blood pressure lowering efficacy of calcium channel blockers for primary hypertension. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD003657. DOI: 10.1002/14651858.CD003657.

3. Ticea, CM, Musini VM, Wright JM. Blood pressure lowering efficacy of beta blockers for primary hypertension. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004806. DOI: 10.1002/14651858.CD004806.

4. World Health Organization. International Clinial Trials Registry Platform (ICTRP). [Online] 2007 [cited 2007 November 17]. Available from: URL: http://www.who.int/ictrp/en/

**Appendix I Trial inclusion form**

DATE OF REVIEW: _____

Reviewer (circle one): BH MP JC MW

| | |
|---|---|
| IDENTIFIER | |
| PUBLICATION DATE | |
| FIRST AUTHOR | |

**INCLUSION CRITERIA:**

| | YES | NO | UNCLEAR |
|---|---|---|---|
| ACE INHIBITOR AS MONOTHERAPY (fixed dose, or forced titration) | ☐ | ☐ | ☐ |
| RANDOMIZED | ☐ | ☐ | ☐ |
| DOUBLE-BLIND | ☐ | ☐ | ☐ |
| PARALLEL PLACEBO ARM | ☐ | ☐ | ☐ |
| HYPERTENSIVE PATIENTS (DBP≥90mm Hg, or SBP≥140mm Hg) | ☐ | ☐ | ☐ |
| TROUGH and/or PEAK SBP and DBP MEASUREMENTS TAKEN AT BASELINE (following washout) AND BETWEEN 3 AND 12 WEEKS OF THE TREATMENT PERIOD | ☐ | ☐ | ☐ |

**INCLUDE** ☐ **EXCLUDE*** ☐

(if "YES" to all above criteria)

* Reason(s) for exclusion:

_____
_____
_____
_____

**Appendix II Data extraction forms for each included trial**

| | | | | | | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| **Systolic Blood Pressure (mmHg)** | Baseline | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | Weighted Mean | | | | | | | | | |
| | BP Change | | | | | | | | | |
| **Diastolic Blood Pressure (mmHg)** | Baseline | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | Weighted Mean | | | | | | | | | |
| | BP Change | | | | | | | | | |
| **Heart Rate** | Baseline | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | ___ wk | | | | | | | | | |
| | Weighted Mean | | | | | | | | | |
| | HR Change | | | | | | | | | |

# DATA EXTRACTION FORM
**(use one form per trial)**

**Administration Details**

Paper title: _____

Paper number: _____

Study ID: _____

Other references to which this trial may link with:

_____

_____

Extractor name:_____

**Characteristics of Included Studies**

**Funding Source (Potential Bias)**

**FOR** **AGAINST** **NO BIAS** **UNCLEAR**

**Methods**

Design of Study:

_____

Method of randomization:

_____

Concealment of randomisation:

_____

Was this concealment adequate/inadequate/unclear?

Blinding:

_____

Description of withdrawals or dropouts:

_____

Jadad score: _____

Additional notes:

_____

_____

**Participants**

Total eligible for inclusion into trial: _____

Total number enrolled into trial: _____

Number in treatment group(s): _____

Number in placebo group: _____

Numbers of withdrawals or dropouts (treatment/control): _____

Numbers completing trial (treatment/control): _____

Age (mean): _____ (range): _____

Sex: _____

Ethnicity: _____

Severity of hypertension (circle one):

**Mild** (DBP 90-105 mmHg)
**Moderate** (DBP 105-115 mgHg)
**Severe** (DBP > 115 mmHg)

Inclusion criteria:

Diagnostic entry criteria: SBP _____ DBP _____

_____

_____

Exclusion criteria:

_____

_____

Baseline characteristics:

_____

Source of participants:

_____

Additional notes:

_____

_____

**Interventions**

Duration of placebo run-in period: _____

Setting:

_____

Types: _____

Duration of treatment: _____

Compliance: Measured? Y/N % Patients compliant _____ How compliant? _____

Goal of therapy: DBP _____ or SBP _____

Additional notes:

_____

**Outcomes**

Outcomes: _____

_____

_____

Adverse events:

_____

_____

_____

Additional notes:

_____

_____

**Cross-over trials**

Run-in phase _____

Treatment & duration _____ Control & duration _____

Washout phase _____

Treatment & duration _____ Control & duration _____

Additional notes:

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_____

Comparison(s) in this trial:

_____

_____