ABSTRACT

Context: Although other factors independent of their blood pressure (BP) lowering effect may contribute to the reduction in morbidity and mortality associated with antihypertensive drugs, efficacy of an antihypertensive treatment is gauged by the magnitude of BP reduction. Diuretics are widely prescribed for hypertension not only as first-line monotherapy but also second-line in combination therapy. Therefore, it is essential to determine the effects of diuretics on BP, heart rate (HR) and withdrawals due to adverse effects (WDAEs) when used second-line for hypertension.

Objectives: 1) To quantify the additional BP reduction of a diuretic as a second-line drug in combination therapy in patients with primary hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg); 2) To determine the additional effects on HR and WDAEs.

Methods: A systematic review of published, double-blind, randomized controlled trials (RCTs) evaluating the BP lowering efficacy of combination therapy (with a diuretic) compared with the respective monotherapy (without a diuretic) for a duration of 3 to 12 weeks in patients with primary hypertension was conducted. Electronic databases were searched for the relevant trials and data were analyzed using Review Manager 5.0.20.

Results: Fifty-three double-blind RCTs evaluating a thiazide in 15129 hypertensive patients (baseline BP of 156/101 mmHg) were included. Hydrochlorothiazide was the thiazide used in 49/53 (92%) of the included studies. The additional BP reduction induced by the thiazide as a second drug was estimated by comparing the difference in BP reduction between the combination and monotherapy groups. Thiazides as a second-line drug reduced BP reduction by 6/3 and 8/4 mmHg at doses of 1 and 2 times the
manufacturer's recommended starting dose respectively. The BP lowering effect was dose related. The effect was similar to that obtained when thiazides are used as a single agent. Only 3 double-blind RCTs evaluating loop diuretics were identified; however, at one times the manufacturer’s recommended dose, the BP lowering effect is similar to thiazides.

**Conclusion:** Thiazides when given as a second-line drug have a dose related effect to lower blood pressure that is similar to when they are used as a first-line drug.
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1 INTRODUCTION

1.1 Hypertension

Elevated blood pressure (BP), commonly called hypertension, is an important health care problem, both in Canada and internationally. The worldwide prevalence of elevated BP is about 26% of the adult population, and the prevalence increases with age [1]. Elevated blood pressure is a major contributor to many cardiovascular diseases (CVD) and has been estimated to contribute 4.5% to the global disease burden [2].

1.1.1 Definition of hypertension

Hypertension has been subdivided into two forms: primary (essential) and secondary hypertension. Primary hypertension accounts for 95-99% of cases and, as the name implies, the cause or causes are unknown (but includes both environmental and genetic factors). On the other hand, hypertension is called secondary when it is a consequence of some biochemical or mechanical pathology that is potentially reversible.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure describes the relationship between BP and risk of CVD as “continuous, consistent, and independent of other risk factors” [3]. The chances of heart attack, heart failure, stroke, and kidney diseases increase with BP increments. Meta-analysis of observational studies showed that the risk of cardiovascular death increases continuously from BP levels of 115 mmHg systolic and 75 mmHg diastolic. At ages 40-69 years, each increment of 20 mmHg in SBP or 10 mmHg in DBP doubles the risk of cardiovascular (coronary heart disease and stroke) morbidity across the entire BP range [4].
However, there is no dividing line between high and normal BP. Arbitrary numerical values have defined hypertension as systolic BP (SBP) of 140 mmHg or greater, and/or diastolic BP (DBP) of 90 mmHg or greater. In 2003, JNC-7 introduced new classification scheme of BP for adults aged 18 years and older [3] (see Table 1.1).

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

JNC-7 suggests that individuals classified as hypertensive (stage1 and stage2) be treated. However, there are disagreements as to the minimum BP level to initiate treatment. As previously defined by Geoffrey Rose, the most appropriate definition of hypertension is “the level at which the benefits of action exceed those of inaction” [5]. Unfortunately, the available data does not allow us to precisely define hypertension using this definition.

**1.1.2 Cardiovascular risk measures**

Both SBP and DBP provide independent clinical information about cardiovascular risk. Data from the long-term Framingham cohort study shows that SBP rises throughout life, while DBP rises until the fifth decade when it starts to fall [6]. This observation has been thought to be due to age-related increase in stiffness of the large arteries. There is still some controversy over whether SBP or DBP is the best predictor of future CVD events. Pulse pressure (PP), the difference between systolic and diastolic pressure, has become increasingly recognized as an independent risk factor for cardiovascular events. Pulse pressure increases progressively with age and the rate of rise of PP accelerates after age 50 years. Analysis of the Framingham Heart Study found that
PP and SBP conferred greater risk of congestive heart failure (CHF) than DBP [7] and neither SBP nor DBP was superior to PP in predicting CHD risk [8]. In a 15 years follow-up cohort study, PP was found to be a risk factor for CHD, CVD, stroke, and all-cause mortality [9]. However, the risk disappeared after adjusting for SBP. Nonetheless, the relative value of SBP, DBP and PP in hypertension treatment is still not clear.

One of the most important characteristics of BP is that it is highly variable between individuals and within individuals. Thus BP fluctuates widely from minute to minute and from hour to hour within an individual. This variability can be assessed in an individual by machines designed to measure BP every 20 minutes over a 24-hour period. Variability using this technique has been shown to independently contribute to the development of end organ damage and cardiovascular events in hypertension [10]. A steep rise in BP around the time of awakening has been associated with a higher risk of acute myocardial infarction (MI) [11]. Daytime SBP variability has been shown to predict progression of early carotid atherosclerosis [12]. Furthermore, larger office BP variability has been found to be associated with a higher risk of stroke as well as MI in elderly patients [13,14].

In the Framingham Heart Study, it was found that heart rate (HR) may be an independent risk factor for CVD in hypertensive patients. Heart rate was found to be a predictor of sudden deaths with average resting HR of 83 beats/min or higher associated with a higher risk of death [15]. Other recent studies have also found significant association between HR and cardiovascular mortality [16, 17]. However, no trial has been designed to specifically evaluate the benefits of lowering HR in terms of cardiovascular outcomes.
1.1.3 BP reduction and its relation to cardiovascular events

Hypertension contributes substantially to the development of cerebrovascular disease, ischemic heart disease, cardiac and renal failure. The main goal of treatment is to reduce the risk of strokes, CVD and death that are associated with elevated BP. Reductions in BP with the use of BP lowering drugs have been associated with reductions in cardiovascular events. A meta-analysis of randomized controlled trials (RCT) using low-dose thiazides (<50mg/day equivalent of hydrochlorothiazide) as compared to placebo reduced SBP/DBP by 13/5 mmHg over a mean duration of 4.1 years resulted in a 11% reduction in mortality, 32% reduction in stroke and 28% reduction in coronary events [18]. The benefit of BP reduction with BP lowering drugs also has been shown to decrease all-cause mortality, as well as cardiovascular morbidity and with greater absolute benefits in older patients [19].

However, there is still no evidence to assess how much BP should be lowered. Excessive lowering can be related to a potential increase in cardiovascular events, referred to as the “J-curve phenomenon”. The critical point of inflection is not yet determined. A recent systematic review has demonstrated that for the general population of patients with elevated BP, treating patients to targets ≤85mmHg or ≤80mmHg as compared to the traditional target of ≤90mmHg is not associated with a reduction in morbidity and mortality [20].

1.1.4 Management of hypertension

When treating hypertension, guidelines recommend that clinicians attempt to achieve a target BP. These BP targets differ in the general population and in patients with
diabetes mellitus or renal disease, but they have not been proven in randomized
controlled trials (see Table 1.2).

Table 1.2: Blood pressure targets of antihypertensive therapy according to several
hypertension guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>General population</th>
<th>With diabetes mellitus or renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 7 2003 [3]</td>
<td>&lt;140/90 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>British Hypertension Society 2004 [21]</td>
<td>&lt;140/85 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>2003 World Health Organization (WHO)/International Society of Hypertension (ISH) [2]</td>
<td>&lt;140/90 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>2004 CHEP [22, 23]</td>
<td>&lt;140/90 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>2007 European Society of Hypertension-European Society of Cardiology [24]</td>
<td>&lt;140/90 mmHg</td>
<td>&lt;130/80 mmHg</td>
</tr>
</tbody>
</table>

1.1.4.1 Non pharmacological treatment

In the algorithm for the treatment of hypertension, therapy begins with lifestyle
modification. Some examples of these lifestyles modifications include weight reduction
in those individuals who are overweight or obese, reduced total fat and saturated fat
intake, reduced dietary sodium intake, increased physical exercise and smoking cessation.
Non-pharmacological treatment may preclude or reduce the need for drug treatment in
some patients. However, pharmacological treatment is frequently required to achieve and
maintain adequate BP control, and a large number of patients will need more than one
drug to achieve BP control.

1.1.4.2 Pharmacological treatment

The first antihypertensive drugs that were used were the veratrum alkaloids in the
1930’s followed by Thiocyanates and ganglion-blocking agents in the 1940’s. Rauwolfia
compounds such as reserpine were introduced in the early 1950’s, followed by the
vasodilator hydralazine, peripheral sympathetic inhibitors such as guanethidine and the
thiazide diuretics. In the 1960’s, central sympathetic inhibitors and beta-adrenergic blocking agents (BB) were introduced. In the 1970’s alpha-adrenergic blocking agents such as prazosin and the angiotensin-converting enzyme inhibitors (ACEI) began to be used and in the 1980’s the calcium channel blockers (CCB) were introduced. The 1990’s saw the addition of the angiotensin II receptor blockers (ARB). The newest class of agents as of this date is the oral renin inhibitor aliskiren, which was approved for treatment of hypertension by US Food and Drug Administration in 2007.

There are a large number of antihypertensive drugs on the market today that lower BP. In general, decisions about which agent or class to use as first-line or second-line in the management of elevated BP should be based on the best available RCT evidence of effectiveness assessing mortality and morbidity outcomes as compared to placebo or no treatment. Four systematic reviews using this evidence to assess the evidence for the five major classes of drugs (thiazide diuretics, ACEI, ARB, CCB and BB) have concluded that the evidence is best for low-dose thiazide therapy [25-28]. No other classes of drugs (ACEI, ARB, BB, CCB and $\alpha$-blocker) were significantly better than low-dose thiazide diuretics for any of the cardiovascular outcomes.

1.1.5 Classes of commonly used anti-hypertensive drugs

Diuretics lower sodium load in the body resulting in reduction of plasma and extracellular fluid volume and BP. Thiazides, such as hydrochlorothiazide or thiazide-like drugs such as chlorthalidone, act primarily on the distal convoluted tubule to block the sodium-chloride co-transporter, inhibiting sodium reabsorption. They have also been shown to decrease peripheral vascular resistance with long term therapy [29]. The BP lowering effect has been suggested to be due to a direct vasodilatory effect independent
of sodium-chloride co-transporter inhibition [30]. Loop diuretics inhibit sodium reabsorption in the ascending limb of the loop of Henle by inhibiting the sodium-potassium-chloride co-transporter. They are the most powerful of the diuretics because they act on the thick ascending limb, which handles the largest fraction of sodium reabsorption. Potassium-sparing diuretics such as amiloride and triamterene inhibit reabsorption at the distal site of the renal tubule and are usually used in combination with other diuretics to reduce the risk of hypokalemia rather than for their BP lowering effect.

The mechanism by which ACEI reduce BP is by blocking the conversion of angiotensin I to angiotensin II which is enzymatically mediated by ACE. Angiotensin II (AII) is a potent vasoconstrictor and also stimulates aldosterone secretion. The administration of ACEI results in vasodilation and dilation of efferent arteriole. Administration of ACEI has also been associated with an increase in bradykinin levels which may contribute to the vasodilatory effect. The production of AII is not completely blocked by ACEI because other enzymes such as tissue-based chymases may facilitate the formation of AII from its precursors.

ARBs were introduced to inhibit the binding of AII to the angiotensin II type 1 (AT1) receptor thereby selectively inhibiting the vasoactive properties of AII. A newer class of agent that also blocks the renin-angiotensin-aldosterone system (RAAS) is the renin inhibitor, aliskiren, which directly inhibits plasma renin activity.

The exact mechanism by which beta-blockers (BB) lower BP has not been established. Blockade of beta receptors (specifically, beta-1 receptors) in the heart reduces heart rate, myocardial contractility and conductivity. Beta-blockers cause a reduction in total peripheral resistance, and inhibit renin release by the kidneys.
Additional vasodilatory effects can be induced by drugs with beta-2 sympathomimetic activity such as pindolol or with combined beta and alpha adrenergic blockade such as labetolol or carvedilol.

Calcium-Channel Blockers (CCB) inhibit calcium entry into vascular smooth muscles by preventing opening of voltage-gated L-type channels. The 3 chemically distinct classes of CCBs are the dihydropyridines (eg nifedipine), phenyalkylamines (eg verapamil) and benzothiazepines (eg diltiazem). The predominant feature of dihydropyridines is arterial dilatation. They are strong vasodilators, acting via relaxation of vascular smooth muscle cells. They have a small negative inotropic effect which is usually overcome by a reflex increase in sympathetic activity. Phenylalkylamines have the most cardiac effect with negative chronotropic and dromotropic effects and the least vasodilatory effects in the group. Benzothiazepines have both cardiac depressant and vasodilator actions and are intermediate between the other two groups.

Centrally-acting drugs inhibit sympathetic outflow via stimulation of central alpha-2 adrenergic receptors or type-1 imidazoline (I-1) receptors located in the nucleus tractus solitarii and the rostral ventrolateral medulla respectively. Methyldopa is the classic example of an alpha-2 agonist and act by stimulating central alpha receptors in the central nervous system, activating inhibitory neurons to produce a decrease in sympathetic outflow, resulting in a decrease in BP. Other drugs such as moxonidine and rilmenidine primarily activate I-2 receptors to inhibit central sympathetic activity. Clonidine shows equal affinity for both receptors.
1.2 Combination therapy

1.2.1 Achieving blood pressure reduction (surrogate outcome)

As mentioned earlier, morbidity and mortality from CVD have been shown to correlate with the level of BP. Another important goal of treating high BP is to prevent further increases in BP.

From large RCTs it has become clear that it is a challenge to reach and maintain BP targets in many patients. BP goals are not likely to be achieved at the starting dose of the first drug used. In fact, monotherapy, even when titrated to high doses, is effective in achieving the standard target BP of $\leq 140/90$ mmHg in only 50% of a population with a baseline DBP of 95-109 mmHg [31]. Low-dose monotherapy, however, remains the accepted initial treatment. If BP is inadequately controlled with the low-dose monotherapy, 3 options are available. The first is to increase the daily dosage of the first drug to the maximum indicated or tolerated dose. The second option is to stop the first drug and do a trial of sequential monotherapy with different classes of drugs in the hopes of finding the drug that lowers BP to the greatest degree in that particular patient. This option would take a considerable length of time. The third option is to add a second drug from another class and at a low dose.

JNC guidelines, which have been published since 1977, first recommended low dose combinations as initial treatment in 1997 [32]. In the most recent publication, JNC7, the guideline states “when BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations” since monotherapy is unlikely to be adequate in such people [3]. As stated in the WHO/ISH guidelines, “It is often preferable to add a small dose of a second
drug rather than increasing the dose of the original drug. This allows both the first and second drugs to be used in a low dose range, which is more likely to be free of side effects [2].

1.2.2 Importance of combination therapy

Hypertension is a multifactorial condition with more than one mechanism involved in its pathogenesis. Modification of one physiologic system by monotherapy usually triggers a compensatory response from another system, limiting the fall in BP. Multiple inhibitory mechanisms are therefore likely to be more effective than a single one. The pharmacological rationale for combining 2 drugs of different classes is that by working at a separate site, different effector pathways can be interfered with. Also, the antihypertensive effectiveness of administration of a single drug might be lessened by counter-regulatory mechanisms in the body which tends to return BP values towards pre-treatment values. By combining antihypertensive agents that possess different mechanisms of action, each component can potentially neutralize or minimize counter-regulatory mechanisms triggered by the other, and thus help to further lower the BP. As well, low doses are generally used in combination therapy, which can minimize both the clinical and metabolic adverse effects seen with higher doses of the individual components. It has also been shown that one component of a fixed-dose combination therapy can effectively counterbalance the tendency of the other to produce adverse effects. For example, the peripheral edema that is associated with CCB occurs less frequently when an ACEI is co-administered [33, 34]

However, there are some potential disadvantages to initiating treatment with fixed-dose combination therapy. If side effects occur, it will not be clear which drug is
responsible. In the event of a side effect both drugs would likely have to be discontinued. Moreover, BP can be controlled with only one drug in some patients even in Stage 2 hypertension; therefore, starting with 2 drugs will lead to unnecessary long-term treatment with the second drug. Finally, by starting with fixed-dose combination therapy, the risk of excessive hypotension is likely increased.

1.2.3 Pharmacological rationale for drug combinations in hypertension

Many choices are available when considering combination therapy for hypertension. The concept is to provide unique complementary benefits for both efficacy and safety or tolerability. Below are described some of the possible advantages of adding diuretic as a second-line drug in combination with other classes of antihypertensive drugs.

By inducing salt excretion and reducing plasma volume, diuretics stimulate the renin-aldosterone-angiotensin system (RAAS). This results in an increased production of renin and angiotensin, thus potentially enhancing the BP lowering effect of ACEI, as these agents directly inhibit the diuretic induced RAAS activity. Thus diuretics added to any of the drugs that block the RAAS system including ACEI, ARB and renin inhibitors is likely a good combination. Diuretics can minimize the risk of hyperkalemia in patients treated with ACEI.

The advantages of adding a diuretic to a BB or CCB are less obvious, however, in each case the drugs are probably working by different mechanisms. Some authors have suggested that the combination of a diuretic and CCB is not rational. These controversies enhance the interest of the proposed systematic review as if they were true, one would
expect the BP lowering effect of the diuretic as second-line drug to be different depending on the first-line drug.

1.2.4 Use of combination therapy

Monotherapy remains the preferred way to initiate drug therapy, and therapy should be individualized according to the individual’s response. A few fixed-dose combinations are available in Canada. However, they are not indicated for initial therapy in patients with mild to moderate hypertension. Dosage must be individualized and each component should be titrated separately. For example, thiazide diuretic should be introduced at a low dose and then progressively increased. It is recommended to use individual drugs (prescribed as separate drugs). Fixed combination tablets would only be an advantage when they supply the particular dose that has been determined to work in an individual [35].

1.2.5 Clinical evidence of combination therapy for treatment of hypertension

It has been shown in many clinical trials that for the majority of hypertensive patients, one drug therapy is insufficient to attain and/or maintain BP goals. Recent studies have shown that most patients require a combination of antihypertensive medications to reach the BP goal.

The HOT study randomized 18790 patients (mean BL 170/105mmHg) to 3 different diastolic BP target groups: ≤90mmHg, ≤85mmHg and ≤80mmHg [36]. At the end of the study (average follow-up time of 3.8years), 78% of the patients were still taking felodipine as baseline therapy, usually together with an ACEI (41%), BB (28%) or diuretics (22%), which reflects the need for combination therapy. In the UKPDS trial, type II diabetic patients randomized to tighter BP control (<150/85mmHg) required an
increased number of antihypertensive agents than did the control group (<180/105mmHg) [37]. At 9 years follow up, about 60% of the patients required 2 or more drugs to maintain BP lower than 150/85mmHg from a baseline pressure of 159/94mmHg. It was also shown in the SHEP trial that a large percentage of participants (elderly with isolated systolic hypertension) required multi-drug therapy to reach goal SBP of a least 20 mmHg reduction from an average baseline BP value of 170/77mmHg [38]. Only 46% of the patients were receiving step 1 monotherapy at the end of 5 years. Similarly, in the SYS-EUR trial (174/86 mmHg), only about 40% of patients reached target BP (reduction of SBP by at least 20 mmHg or to less than 150 mmHg) on monotherapy at the end of 4 years follow-up [39]. These trials confirmed that less than 50% of patients can be controlled by monotherapy and the rest will eventually require additional drugs added to their treatment regimen. At least one second- or third- line drug was necessary to achieve modern treatment targets and the necessity of combination therapy has also been shown in many other trials as well [40, 41, 42]. Although patients were usually started on a one-drug therapy, none of these trials were strictly a trial of monotherapy because add-on was permitted and a substantial proportion of patients received more than one drug at the end of the trial.
1.3 References


2 SYSTEMATIC REVIEW

2.1 What are systematic reviews and why do we need systematic reviews?

One of the methods to incorporate research evidence into clinical decision making is the systematic review [1]. A systematic review is a literature review that addresses a specific research or clinical question, and in which evidence is systematically identified, appraised, and summarized according to pre-defined, explicit methods. Because of the overwhelming and ever-increasing amount of research information, it is difficult for health professionals, policy makers and consumers to stay informed and up-to-date in making informed health-related decisions. Therefore, systematic reviews are needed to efficiently integrate existing information and provide data for rational decision making. Systematic reviews can assess consistency of study findings and whether the scientific findings can be generalized [2].

Systematic reviews can be qualitative or quantitative. It is called a meta-analysis when statistical methods are used to generate a pooled estimate of a treatment effect or other end points. Combining the data from individual studies quantitatively using statistical methods increases the statistical power of the analysis and the precision of the treatment effect size [3].

Most review articles are narrative rather than systematic, and generally cover a broader scope within a specific topic. Both narrative and systematic reviews are retrospective studies and, therefore, are subject to bias. Therefore, the process of conducting a review must be rigorous and according to a well-defined methodology. The main and most crucial difference between a narrative and systematic reviews is the extent to which review methods have been used to minimize errors and bias. Narrative reviews
are most often written by experts in a given field using partial selection of the literature that support their preconceived opinions and exclude those with conflicting views. A narrative review is unscientific because it lacks formal tools to identify, evaluate, and synthesize the research evidence, making it impossible to replicate and the validity of the conclusions and recommendations questionable.

In contrast to traditional narrative reviews, systematic reviews are designed to minimize bias and random errors (and ensuring their reliability) by employing explicit methods which are clearly stated. The approach used to identify and critically appraise all relevant studies, and to extract and synthesize data is pre-specified and transparent to allow reproducibility by others. Nevertheless, all reviews are retrospective, and hence subject to bias. Meta-analysis of primary studies could produce an inflated effect size if publication bias is present where positive-results studies are more likely to be published (sometimes more than once) than negative-result studies. There have been numerous methods to detect publication bias and statistical and remodeling methods are available to correct for this type of bias and to provide a more accurate estimate of the true effect size [4, 5, 6]. Other bias such as selection and observer bias can be minimized by having multiple reviewers to select the studies and extract the data.

2.2 The Cochrane collaboration

The Cochrane collaboration is an international organization that aims to produce, maintain, and disseminate up-to-date systematic reviews on all areas of health care. Founded in 1993, it is named after the British epidemiologist, Archie Cochrane, and is based on 10 key principles: collaboration, building on the enthusiasm of individuals,
avoiding duplication, minimizing bias, keeping up to date, striving for relevance, promoting access, ensuring quality, continuity, and enabling wide participation [7].

Cochrane reviews are published in the Cochrane Database of Systematic Reviews section of the Cochrane Library (updated quarterly). Because they are published electronically, it allows reviews to be replaced with updated version in response to new evidence or comments and criticisms from readers. The standardized framework of preparing a systematic review within the Cochrane collaboration can be found in the Cochrane handbook [2].

2.3 Aim of this systematic review

The issue of which antihypertensive agent should be used in first-line treatment has been controversial for almost decades. Not surprisingly, there are also controversies as to the optimal drug combinations in terms of long-term outcomes (taking into consideration BP control and/or specific effects of specific drugs). However, all these studies underpin the importance of combination therapy in hypertension treatment. Therefore it is important to assess the BP lowering efficacy of all possible combinations. A systematic review published by Law and Wald has attempted to determine the BP lowering efficacy of five classes of antihypertensive agents (thiazides, ACEI, ARB, BB, and CCB as monotherapy and of 2 or more drugs in combination [8]. The authors analysed data from 50 studies to assess whether the combined effect of two drugs of different classes was additive with respect to BP reduction. The placebo-corrected mean weighted BP reduction of the ‘first drug’ monotherapy group, the ‘second’ drug monotherapy group, and the combination group (‘first’ and ‘second’ drugs given together) were evaluated. The review demonstrated that there was no statistical
significant difference between the expected BP reduction (sum of the first and second drugs alone) and the observed BP reduction in the combination group, concluding that the combination of major groups of antihypertensives was strictly additive. The authors also suggested that the effect of three drugs in combination would also be additive based on no trial assessing the BP effect of 3 drugs in combination. The authors did not attempt to compare the dose-related additional BP lowering efficacy of each major drug class separately as second-line therapy. This thesis is a systematic review designed to determine the additional BP lowering efficacy of second-line diuretics in patients with primary hypertension. Unlike Law and Wald’s review, it is not limited to RCTs with a placebo arm. Focussing on diuretics as second-line alone, this review has included 56 trials, more than what was identified by Law and Wald’s review. This current review will be able to quantify the additional reduction in SBP/DBP one would expect to achieve with the addition of a diuretic as the second drug in combination.

A well-formulated research question includes five basic components: 1) types of study design 2) types of participants 3) types of interventions (exposure) 4) types of outcomes, and 5) types of control (any comparators where relevant). In this present review, the research question is: “In double-blind randomized controlled trials, what is the magnitude of additional BP reduction induced by diuretic given as a second drug in combination therapy in primary hypertensive patients?”

2.4 Protocol

The protocol of this systematic review was finalized on April 2008 and published in Issue 2, 2008 of the Cochrane Library [9] to outline the predefined procedural methods that would be followed in conducting this review.
2.4.1 Objectives

Primary Objective

To quantify the additional reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of a diuretic as second-line therapy in patients with primary hypertension.

Secondary Objectives

1. To determine the effects of a second-line diuretic on variability of blood pressure.
2. To determine the effects of a second-line diuretic on pulse pressure (PP).
3. To quantify the effects of a second-line diuretic on heart rate (HR).
4. To quantify the effects of a second-line diuretic on withdrawals due to adverse effects (WDAE).

2.4.2 Methodology

2.4.2.1 Types of studies

Only randomized controlled trials (RCTs) were included and the study must have met the following criteria:

- Double-blind
- Parallel design with random allocation treatment groups
- Washout period of at least 2 weeks prior to randomization
- Office BP measurement at baseline (following washout) and at one or more time points between 3 to 12 weeks post-treatment

2.4.2.1.1 Why are only randomized controlled trials included?

In RCTs, patients are randomly assigned to receive one of two or more clinical interventions. With random assignment, each patient has an equal probability of being assigned to any given group. This helps to eliminate selection bias and balance known
and unknown baseline confounding factors, minimizing their influence on the outcomes of the study. Using this approach, any differences in outcomes can be attributed to the differences in the intervention received (study treatments). However, selection bias can still be introduced in RCTs if the statistical analysis of the study is not based on an intention-to-treat analysis. If some patients are excluded from the analysis, the baseline prognostic factors between the groups at baseline might no longer be evenly distributed, which could lead to potential bias.

2.4.2.1.2 Why is blinding (masking) necessary?

Blinding helps to reduce bias after the assignment of treatments. Studies that will be included in this review will be double-blind RCTs in which the patients and the investigators are unaware of which treatment each patient is receiving. Knowledge of treatment assignment could lead to alteration of the study results arising from the participants, care-provider or the people who assess the outcomes. Double-blinding ensures that their preconceived views cannot systematically bias the assessment of outcomes. Blood pressure, the primary outcome in this review, is highly subject to observer bias when the BP is measured by auscultation.

2.4.2.1.3 Why is a baseline measurement subsequent to a washout/placebo run-in period important?

A washout period (single-blind placebo run-in) helps to eliminate carry-over effects from previous drug therapy before the clinical trial is commenced. In trials with cross-over design, a washout period would also be necessary between different treatment periods for the same reason. Before randomization, data at the end of the run-in are collected providing the baseline data for the patients (i.e. baseline BP and HR data). The
washout period also serves to screen out ineligible patients. Patients who did not meet the inclusion BP criteria at the end of the washout period are not entered into the study.

2.4.2.1.4 Why is the 3 to 12 week window selected?

Data obtained within the 3 to 12 week treatment period will be used in the analysis for this systematic review. The window period was selected based on a previous systematic review. A minimum of 3 weeks was required for the maximum effect of the drugs to be observed. An upper duration limit of 12 weeks was chosen to maximize the number of patients included in the analysis as withdrawals rate increases with the duration of the therapy. Also, with longer duration trials, patients are more likely to receive additional drugs or dose titration if they continue to fail to achieve the target BP level. Trials meeting the inclusion criteria but with greater than 12 weeks duration will be included only if they provided data for the 3 to 12 week treatment period.

2.4.3 Types of participants

Men and non-pregnant women at least 18 years old with an office baseline SBP of at least 140 mmHg and/or DBP of at least 90 mmHg. Participants with significant renal failure or creatinine levels greater than 1.5 times the normal value were excluded because these patients usually require dose adjustments. Patients were not restricted by other baseline risks or co-morbid conditions.

2.4.4 Types of interventions

Combination therapy with a diuretic plus other non-diuretic antihypertensive drug(s) versus other non-diuretic antihypertensive drug(s) alone. The addition of a diuretic must have been the only difference between the combination and monotherapy groups. In the case of fixed-dose combination, the pill should be identical in appearance
and taste to the individual components; in other cases where drugs are administered separately in the combination group, the monotherapy group should receive a matching placebo (double-dummy design).

The diuretics that were included in this review were the loop diuretics and the thiazides. Potassium-sparing diuretics and aldosterone antagonists were not included in this review. The non-diuretic component included pharmacological agents in the following drug classes: Angiotensin-converting enzyme inhibitor (ACEI); calcium channel blocker (CCB); beta-blocker (BB); angiotensin receptor blocker (ARB); renin inhibitor (RI); and centrally-acting drugs (CAD) (but limited to guanabenz, rilmenidine, clonidine, moxonidine, methyldopa and guanfacine). All dosages and combinations of these drugs were considered. Trials in which titration to a higher dose was based on BP response were excluded. For forced titration trials, data from the lowest dose given within 3 to 12 weeks period were extracted.

2.4.5 Types of outcome measures

Primary Outcome

- Additional reduction in SBP and DBP with second-line diuretics. This was the difference in change from baseline in trough SBP and DBP at 3 to 12 weeks between the combination and monotherapy groups. If BP measurements were available at more than one time during the 3 to 12 week treatment period, the weighted mean of the BP data were used in this review.

Secondary Outcomes

- Change in standard deviation of BP with combination therapy as compared to monotherapy
• Incidence of withdrawals due to adverse effects with combination therapy as compared to monotherapy
• Change in heart rate with combination therapy as compared to monotherapy
• Change in pulse pressure with combination therapy as compared to monotherapy

2.4.6 Search methods for identification of studies

The following electronic databases were searched for relevant RCTs: MEDLINE (1966 to July 2008), EMBASE (1988 to July 2008), and the Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, Issue 2). We also searched the bibliographic citations of included studies and review articles for relevant studies not already identified by our comprehensive search. Authors were contacted to retrieve missing information. No language restrictions were applied.

The structure of the electronic search strategy was based on the standard search strategy of the Hypertension Review Group, and modified and expanded with additional terms to identify RCTs assessing a diuretic combined with other antihypertensive drug classes for the treatment of primary hypertension (see Appendix A).

2.4.7 Study selection

The titles and/or abstracts obtained from the search strategies were screened by one reviewer. During the initial abstract screening, those studies that were irrelevant to the review or clearly did not meet the inclusion criteria were rejected. The remaining trials were obtained in full text to assess whether they met the pre-specified inclusion criteria. Trials were then assessed for inclusion eligibility by two reviewers independently. Any discrepancies were resolved by a third reviewer. Trials with multiple publications were counted only once.
2.4.8 Data extraction

Data were extracted independently by two reviewers using a standardized form, and then cross-checked. All numeric calculations and graphic interpolations were confirmed by a second person.

The position of the patient during BP measurement may affect the BP lowering affect. When measurements were reported in more than one position, the order of preference was: 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 standard deviation of the change in BP or heart rate (HR), 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. Standard deviation of change in BP/HR from a different position than that of the BP/HR data used.
3. Standard deviation at the end of treatment measured from a different position than that of the BP/HR data used.
4. Standard deviation at baseline (except if this measure was used for entry criteria).
5. Mean standard deviation of change from other trials using the same drug and dose.

2.4.9 Risk of bias assessment

The risk of bias in included studies was assessed using the Cochrane Collaboration's recommended tool, which is a domain-based critical evaluation of the
following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other sources of bias [2].

2.4.10 Data analysis and statistical consideration

Data synthesis and analyses was done using the Cochrane Review Manager software, RevMan 5.0.20. Data for changes in BP and HR were combined using a weighted mean difference method. WDAE was analyzed using relative risk, risk difference, and number needed to harm.

If possible, subgroup analyses were used to assess the results for specific categories of participants:
1) Age: adults (18-69 yrs), older people (70 years and older)
2) Race: White; Black; other
3) Baseline severity of hypertension: mild; moderate; severe
4) Drug classes: The different classes of drug used in combination with a diuretic

2.4.11 Direct and indirect comparisons

When possible, direct and indirect comparisons of effect sizes were performed between different doses of diuretics. In the direct method, only trials that randomized patients to various doses of diuretics in combination therapy were included in the analysis. In the indirect method, an "adjusted indirect comparison" and the associated standard error were calculated using the methods previously described by Bucher 1997 and Song 2003 [10, 11].

A p-value less than 0.05 was considered statistically significant for all comparisons. Tests for heterogeneity of the treatment effect between trials were made using a standard chi-square statistic for heterogeneity. The fixed effect model was applied
to obtain summary statistics of pooled trials, unless significant between-study heterogeneity was present, in which case the random effects model was used. This model provides a more conservative statistical comparison of the difference between combination therapy group and monotherapy group 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 used as the best estimate because of the tendency of smaller trials, which are more susceptible to publication bias, to be over-weighted with a random effects analysis.
2.5 References


3 RESULTS

3.1 Search findings

The search strategy was developed to identify all double-blind, RCTs that assess the BP lowering efficacy of combination therapy versus their individual components in hypertensive patients. A search was performed to identify relevant trials for this review, and also for 3 other reviews which addressed similar research questions but focused on ACE inhibitors [1], angiotensin receptor blockers [1], renin inhibitors [1], beta blockers [2] and calcium channel blockers [3] as second-line drugs in combination therapy. In total, this search strategy identified 25084 citations and only 56 (0.2%) trials met the inclusion criteria and had data suitable for analysis in this systematic review (Figure 3.1). Forty-four other studies that met the inclusion criteria of this review were excluded because they did not provide extractable data (see section 3.1.2).
3.1.1 Characteristics of included studies

All the included studies were of parallel design. Of all the 56 included studies, 53 (95%) were published in English, 1 in German, 1 in French, and 1 in Spanish. Funding sources were only reported in 28 (50%) of the included studies. All the studies that reported funding source were industry funded. Fifty-three of the included studies assessed thiazides (49 with hydrochlorothiazide, 2 with indapamide, 1 with clopamide, and 1 with
chlorthalidone) and 3 included studies assessed loop diuretics (2 with piretanide and 1 with frusemide). There were no studies found that assessed the effect of a diuretic as a third-line drug. There were 7 studies that assessed the effect of a thiazide and a potassium-sparing diuretic combination as second-line therapy but these studies were excluded from this review.

Table 3.1 summarizes the characteristics of each included study. Each study was assigned a unique identifier consisting of either the surname of the first author followed by the year of publication or the acronym of the trial name.

**Table 3.1 : Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td>Asplund 1981 [4]</td>
<td><strong>Design:</strong> 12 weeks double-blind, parallel study after 4 weeks run-in period with placebo. Randomized (methods not described)</td>
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<tr>
<td></td>
<td><strong>Participants:</strong> 75 patients with supine BP &gt;160/95 mmHg at end of run-in period. Age range: 21-71 (mean: 48 yrs)</td>
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<td><strong>Interventions:</strong> 3 treatment groups (bid):</td>
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<td></td>
<td>Monotherapy: Metoprolol 100mg (M100); HCTZ 12.5mg (H12.5)</td>
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<td>Combination: Fixed-ratio M100/H12.5</td>
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<td>The dosage was 1 tablet morning and evening in all cases.</td>
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<td></td>
<td><strong>Primary and Secondary Outcomes:</strong> Standing SBP and DBP and HR (timing of measurement not reported), WDAE</td>
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<tr>
<td></td>
<td><strong>Funding Source:</strong> Not reported</td>
</tr>
<tr>
<td>Benz 1998 [5]</td>
<td><strong>Design:</strong> 8-week, double-blind, placebo-controlled parallel study after washout period of at least 2 weeks and single-blind placebo treatment for 2-4 weeks; randomized (methods not described)</td>
</tr>
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<td></td>
<td><strong>Participants:</strong> 871 adult out-patients with sitting diastolic BP 95-115 mm Hg. Difference between enrolment and randomization &lt;=10mm Hg. Age: &gt;18 (range 22-26, mean 52); 58% men. 75% white, 14% black, 11% other.</td>
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<td>Study</td>
<td>Study Description</td>
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<tr>
<td></td>
<td><strong>Interventions</strong>: 9 treatment groups o.d.:</td>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td>Monotherapy: valsartan 80 or 160mg, Hydrochlorothiazide 12.5 or 25mg</td>
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<tr>
<td></td>
<td>Combination therapy: valsartan 80mg/ hydrochlorothiazide 12.5mg (V80/H12.5), V160/H12.5, V80/H25, V160/H25.</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Sitting trough SBP and DBP; HR (no quantitative data), WDAE</td>
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<td></td>
<td><strong>Notes</strong>: Efficacy analyses: 865 patients with post-randomization measurements 867 patients included in safety analysis 792/871 patients completed the trial 41 WDAE (the number of WDAE in each group is not reported) &quot;No statistically or clinically significant differences between groups in sitting or standing pulse rate&quot;</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source</strong>: Novartis</td>
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</table>

<p>| Bermudez 1982 [6]      | <strong>Design</strong>: 8 week comparative, double-blind, multi-center study after a 2-week placebo run-in period. Data extracted at week 4. Dose is doubled after week 4 if DBP &gt; 90 mmHg. |
|                        | <strong>Participants</strong>: 76 ambulatory patients with DBP of 95 to 130 mmHg after 2 weeks of placebo run-in. Mean age: 47 years. 24% male.                                              |
|                        | <strong>Interventions</strong>: 3 treatment groups (od):                                                                                                                                   |
|                        | Monotherapy: Oxprenolol 160mg (O160); Chlorthalidone 20mg (C20)                                                                                                                 |
|                        | Combination: O160/C20                                                                                                                                                           |
|                        | <strong>Primary and Secondary Outcomes</strong>: Trough supine SBP and DBP and HR; WDAE                                                                                                    |
|                        | <strong>Notes</strong>: Efficacy analysis in 75 patients; Safety analysis in all 76 patients                                                                                                  |
|                        | <strong>Language</strong>: Spanish                                                                                                                                                           |
|                        | <strong>Funding Source</strong>: Not reported                                                                                                                                             |</p>
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<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td>Primary and Secondary Outcomes: Trough supine SBP and DBP and HR; WDAE</td>
<td>Notes: Efficacy analysis in 75 patients Safety analysis in all 76 patients Language: Spanish Funding Source: Not reported</td>
</tr>
<tr>
<td>Brown 1990 [7]</td>
<td>Design: 4-week double-blind study after a 2 week placebo period. Randomized (methods not described) Participants: 40 patients, aged between 18 and 70 yrs with supine diastolic BP between 95 and 115mmHg after placebo phase. Mean age 58yrs. 19 male and 21 female. Interventions: 4 treatment groups: Placebo Monotherapy: Perindopril 4mg/day (P4); HCTZ 25mg/day (H25) Combination: P4/H25 (tablets were identical in appearance) Primary and Secondary Outcomes: Trough (24 hours post-dose) standing SBP and DBP; WDAE; HR (no quantitative data) Notes: No dropouts in study. “Heart rate was not influenced by any of the drug treatments used” Funding Source: Not reported</td>
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<tr>
<td>Camera 1995 [8, 9]</td>
<td>Design: 8-week double-blind active treatment following a 4-week single-blind placebo treatment. Randomized (methods not described). Participants: 149 patients, aged between 30 and 70 years, with uncomplicated mild to moderate hypertension (DBP 90-114 mmHg). 42% men. Mean age: 53 years.</td>
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<td>Study</td>
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| Chadha 1983 [10]   | **Design**: 6 week double-blind trial after a 4-week placebo washout period. Randomized (methods not described). After 4 weeks of therapy, a second dose in the evening was added if DBP >95mmHg. On admission a low salt diet of 3-6g NaCl was prescribed. Data up to 4 weeks will be used in the review.  
**Participants**: 41 adult outpatients, aged 30-70 years, with DBP between 95 and 120mmHg at the end of placebo run-in.  
**Interventions**: 3 treatment groups (o.d.): Monotherapy: Penbutolol 40mg (P40); Frusemide 40mg (F40)  
Combination: P40/F40  
**Primary and Secondary Outcomes**: Erect SBP and DBP and HR (timing of measurement not reported)  
**Notes**: Number of patients included in efficacy analysis was not reported. It was assumed in this review that all patients were included in the efficacy analysis  
Funding Source: Not reported |
| Chrysant 1994 [11] | **Design**: "randomization process failed to produce groups which were strictly comparable in terms of the level of hypertension"  
**Participants**: 505 patients whose sitting diastolic BP was 100-114mmHg after placebo period. 311 (62%) men. Mean age: 53 yrs. 67% white. 24% black. |
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<th>Study</th>
<th>Study Description</th>
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<tr>
<td><strong>Interventions:</strong> 6 treatment groups (od): Placebo</td>
<td><strong>Primary and Secondary Outcomes:</strong> Trough (24±2 hours post-dose) sitting SBP and DBP</td>
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<tr>
<td>Monotherapy: Lisinopril 10mg (L10); HCTZ 12.5 mg (H12.5); H25</td>
<td><strong>Notes:</strong> 467 patients completed the study.</td>
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<tr>
<td>Combination: L10/H12.5; L10/H25</td>
<td>Efficacy analysis: ITT (467 patients)</td>
</tr>
<tr>
<td><strong>Notes:</strong> 467 patients completed the study.</td>
<td>Funding Source: ICI Pharmaceuticals Group</td>
</tr>
<tr>
<td>Chrysant 1996 [12]</td>
<td><strong>Design:</strong> 6-week, double-blind, parallel multicenter study after a 1-4 week placebo run-in period. Randomized (methods not described).</td>
</tr>
<tr>
<td><strong>Participants:</strong> 334 outpatients, aged 18 years or older, with sitting diastolic BP between 95 and 114mmHg at two consecutive visits during the placebo phase, with a difference of 10mmHg or less at the two visits. 210 (63%) men. 26% black. 70% white. Mean age: 53.5yrs.</td>
<td><strong>Interventions:</strong> 8 treatment groups (o.d.): Placebo Monotherapy: Benazapril HCl 20mg (B20); HCTZ 25mg (H25) Combination: B5/H6.25; B10/H12.5; B20/H25; B20/H6.25; B5/H25 Study medication was provided in capsules of identical appearance.</td>
</tr>
<tr>
<td><strong>Primary and Secondary Outcomes:</strong> Trough (22 to 26 hrs post-dose) sitting SBP and DBP; HR (no quantitative data)</td>
<td><strong>Notes:</strong> Efficacy Analysis: all patients randomized to receive double-blind treatment with last post randomization measurement carried forward (n=328). 301/334 patients completed the study. Safety analysis in 334 patients “No clinically important changes from baseline were reported in mean pulse for any treatment group”</td>
</tr>
<tr>
<td><strong>Funding Source:</strong> Ciba Pharmaceuticals</td>
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<tr>
<td>Study</td>
<td>Study Description</td>
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</table>
| Chrysant 2004 [13] | **Design:** 8-week double-blind factorial design study after a 4 week placebo run-in period.  

**Participants:** 502 patients with average sitting DBP $\geq 100$mmHg and <=115mmHg at both week 3 and week 4 placebo run-in visits and a difference of <=7mmHg between the two measurements. 55.6% male and 74.1% white. Mean age: 53years.  

**Interventions:** 12 treatment groups (od):  
Placebo  
Monotherapy: Olmesartan 10, 20 or 40mg; Hydrochlorothiazide 12.5 or 25mg  
Combination: All possible combinations  

**Primary and Secondary Outcomes:** Trough sitting SBP and DBP; percentage of WDAE  

**Notes:** 451 patients completed the study.  
Percentage of WDAE was low (2%)  

**Funding Source:** Sankyo Pharma Inc. |
| Drayer 1995 [14]   | **Design:** 8-week double-blind, multicenter, placebo-controlled, parallel group study after a 4-week placebo run-in phase. Randomized (methods not described)  

**Participants:** 413 ambulatory outpatients with sitting DBP between 95 and 114 mmHg after placebo period.  

**Interventions:** 9 treatment groups (od):  
Placebo  
Monotherapy: Hydrochlorothiazide 12.5mg (H12.5); Moexipril 3.75mg (M3.75); M7.5; M15; M30  
Combination: H12.5/M3.75; H12.5/M7.5; H12.5/M15  

**Primary and Secondary Outcomes:** Trough sitting SBP and DBP; WDAE; HR (no quantitative data) |
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<th>Study</th>
<th>Study Description</th>
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| Fernandez 1994 [15]   | **Notes**: 391 patients completed the study  
"no significant changes in HR within any of the combination or monotherapy treatment groups"  
**Funding Source**: Not reported                                                                                                  |
|                       | **Design**: 8-week double-blind. Randomized (method not described)                                                                                                                                                 |
|                       | **Participants**: 67 patients of either sex 18 to 75 yrs of age with seated diastolic BP >=95 and <=110 mm Hg. Mean age: 53 yrs. 23 (34%) male.                                                                    |
|                       | **Interventions**: 4 treatment groups (o.d):  
-placebo  
-monotherapy: fosinopil 20mg (F20), hydrochlorothiazide 12.5mg (H12.5)  
-combination: F20/H12.5  
**Primary and Secondary Outcomes**: Sitting trough SBP and DBP (24±3hrs after previous dose)  
**Notes**: Efficacy Analyses: ITT (blood pressure data at baseline and at least one follow-up visit) = 67  
Assume WDAE = 2 (at week 6, two patients were withdrawn from the study due to adverse events)  
**Funding Source**: Not reported |
| Frei 1994 [16]        | **Design**: 8-week multicenter, DB, placebo-controlled, parallel-group trial after a 4-week placebo run-in phase. Randomized (methods not described)                                                           |
|                       | **Participants**: 161 patients with DBP >=95 and <=114mmHg, and SBP <=240mmHg. Mean age 55.1yrs.                                                                                                                     |
|                       | **Interventions**: Treatment groups (od):  
Placebo  
Monotherapy: Moxonidine 0.4mg (M0.4); HCTZ 25mg (H25)  
Combination: M0.4/H25  

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<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
</tr>
</thead>
</table>
| Frishman 1994 [17]  | **Design**: 12-week double-blind, placebo-controlled, multicenter 3x4 factorial trial after a 4-6 week single-blind placebo phase. Randomized (methods not described).  
**Participants**: 512 patients aged 21 years or older with mild to moderate essential hypertension whose weight was within 35% of the ideal for height and frame were eligible for randomization. Mean sitting diastolic BP was stable and between 95 and 115 mmHg (inclusive). 364 (71%) male. 366 (71%) non-black.  
**Interventions**: 12 treatment groups (od):  
Placebo  
Monotherapy: HCTZ 6.25mg (H6.25); H25; Bisoprolol 2.5mg (B2.5); B10; B40  
Combination: H6.25/B2.5; H6.25/B10; H6.25/B40; H25/B2.5; H25/B10; H25/B40  
**Primary and Secondary Outcomes**: Trough (24 hours post-dose) sitting SBP and DBP; WDAE  
**Notes**: The primary efficacy variable was defined a priori as the change from baseline sitting diastolic BP in patients evaluable at weeks 3-4. (n=465) 403/512 patients completed the study.  
**Funding Source**: American Cyanamid Co. |
**Participants**: 547 patients, 21 years or older with sitting DBP between 95 and 115mmHg on 3 consecutive weekly visiting during placebo period.                                                                                     |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
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|       | **Interventions**: 4 treatment groups (od):  
|       | Placebo  
|       | Monotherapy: Bisoprolol 5mg (B5); HCTZ 6.25mg (H6.25)  
|       | Combination: B5/H25  
|       | **Primary and Secondary Outcomes**: Trough (24hours post-dose) sitting SBP and DBP and HR; WDAE  
|       | **Notes**: 509/547 patients for efficacy analysis [310 (61%) male. 82% non-black, 18%black]  
|       | **Funding Source**: American Cyanamid Company |
| Genthon 1994 [19] | **Design**: 8-week double-blind, multicentre, parallel-group trial following a 4-week, single-blind, placebo run-in period. Randomized (methods not described)  
|       | **Participants**: 660 patients of either sex, aged between 18 and 75 years, with supine DBP of more than 95mmHg but less than 115mmHg after placebo run-in. Systolic BP <=200mmHg. Women of childbearing potential were excluded.  
|       | **Interventions**: 3 treatment groups (o.d.):  
|       | Monotherapy: Ramipril 2.5mg (R2.5); HCTZ 12.5mg (H12.5)  
|       | Combination: R2.5/H12.5  
|       | **Primary and Secondary Outcomes**: Trough (22-26 hours post dose) supine SBP and DBP; WDAE; HR (no quantitative data)  
|       | **Notes**: Efficacy Analysis: per-protocol analysis which excluded certain protocol violators (n=535 because 125/660 patients did not strictly fulfill the inclusion criteria for supine DBP during the placebo run-in).  
|       | 624/660 patients completed the study.  
|       | “Whilst heart rate was stable in all groups throughout the study, there was a slight decrease in all groups”  
<p>|       | <strong>Funding Source</strong>: Laboratoires Hoechst |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart 1991</td>
<td><strong>Design:</strong> 8-week double-blind, parallel-group multicentre study after a 2-week single-blind placebo run-in period. Randomized (methods not described)</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> 299 patients aged 65-80 years with a sitting DBP of 100-120mmHg (inclusive) during the placebo run-in period. 123 (41%) male. Mean age: 71 yrs.</td>
</tr>
</tbody>
</table>
|            | **Interventions:** 3 treatment groups (od):  
|            | - Monotherapy: Lisinopril 20mg (L20); HCTZ 12.5mg (H12.5)  
|            | - Combination: L20/H12.5  
|            | **Primary and Secondary Outcomes:** Trough (24-28 hours) sitting SBP and DBP; WDAE  
|            | **Notes:** 278/299 patients completed the study  
|            | Efficacy analysis: Based on "per protocol analysis". Excluded were patients where the number of tablets returned was less or more than expected or if there was any deviation from the protocol during the interval between the last dose of medication and BP measurement (By 8 weeks of treatment 125 patients had complied with the protocol).  
|            | “There was no statistically significant difference between the groups for HR”  
|            | 2 patient died during the study "for reasons unrelated to the trial medication"  
|            | **Funding Source:** Not reported                                                                                                                                                                                                                                                                 |
| Homuth 1993 | **Design:** 6-week multiclinic, double-blind, placebo-controlled trial after a 2-week placebo run-in period. Randomized (methods not described)                                                                                                                                                                                                                           |
|            | **Participants:** 480 patients, aged 21 to 65, with a diastolic BP between 100 and 115mmHg after run-in period. 295 (74%) men. Mean age: 47 years.                                                                                                                                                                                                                       |
|            | **Interventions:** 12 groups (od):  
|            | - Placebo  
|            | - Monotherapy: Ramipril 2.5mg (R2.5); R5; R10; Piretanide 3mg (P3); P6  
|            | - Combination: R2.5/P3; R2.5/P6; R5/P3; R5/6; R10/P3; R10/P6
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<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
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</table>
|             | **Primary and Secondary Outcomes**: Trough (24hrs post-dose) SBP and DBP; WDAE  
|             | **Notes**: Efficacy Analysis: ITT basis: Any randomized patient meeting the inclusion criteria with any post-randomization data during the double-blind treatment phase.  
|             | 452/480 patients completed the study  
|             | BP data obtained from fig 1 and fig 2 on page 669. The position of measurement was not mentioned.  
|             | **Funding Source**: Cassella AG  
| Kayanakis 1987 [22] | **Design**: 8-week multicenter, double-blind, placebo-controlled parallel study after a 2 week placebo run-in period; randomized (method not described)  
|             | **Participants**: 211 men and women aged 20-70 yrs with diastolic BP between 95 and 120 mm Hg and systolic BP between 160 and 200mmHg. Mean age: 53 yrs. 56% male  
|             | **Interventions**: 4 groups (od):  
|             | Placebo  
|             | Monotherapy: Captopril 50mg (C50) ; HCTZ 25mg (H25)  
|             | Combination: C50/H25  
|             | **Primary and Secondary Outcomes**: Supine trough SBP and DBP (20-24 h after the last medication); HR (data not shown); WDAE  
|             | **Notes**: 205 completed the study; statistical analysis on 211 who entered double-blind study  
|             | “Heart rate did not change significantly with either treatment  
|             | **Funding Source**: Not reported  
<p>| Kellaway 1993 [23] | <strong>Design</strong>: 8-week multicenter, double-blind, parallel group study after a 2-week single blind placebo run-in period. Randomized (method not described). Non responders at week 4 received double dose of cilazapril. Data up to week 4 were used. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
</tr>
</thead>
</table>
| **Participants:** 69 patients, aged 18 to 75 yrs, with sitting DBP 95-115 mmHg at end of placebo run-in. | **Interventions:** 2 treatment groups (od):  
Monotherapy: Cilazapril 2.5mg (C2.5)  
Combination: C2.5/HCTZ12.5  

**Primary and Secondary Outcomes:** Sitting SBP and DBP (timing of measurement not reported); WDAE; heart rate (data not shown)  

**Notes:** 87 patients entered run-in phase (51% male; mean age: 54.6yrs)  
Efficacy analysis not described (n=57)  
“Heart rate did not differ significantly at week 4 and 8”  

**Funding Source:** Not reported |

| Kochar 1999 [24] | **Design:** 8-week double-blind, placebo-controlled parallel study after a 4-5 week single-blind placebo phase (conducted at 46 sites in the US); randomized (method not described)  

**Participants:** 683 men and women (>=18yrs) with seated diastolic BP between 95 and 110 mm Hg at weeks 3 and 4 or optional week 4 and 5 of placebo lead in phase. Difference between weeks of <=8mm Hg. Mean age: 55yrs. 65% male, 85% white and 48 (14%) black.  

**Interventions:** 4x4 factorial design (od)  
Placebo  
Monotherapy: Irbesartan 37.5mg (I 37.5); I 100; I 300; Hydrochlorothiazide 6.25 (H 6.25); H 12.5; H 25  
Combination: I 37.5/H 6.25; I 37.5/H 12.5; I 37.5/H 25; I 100/H 6.25; I 100/H 12.5; I 100/H 25; I 300/H 6.25; I 300/H 12.5; I 300/H 25  

**Primary and Secondary Outcomes:** trough (24+-2h after the last dose) sitting SBP and DBP; WDAE  

**Notes:** Analyses of efficacy assessments included data for all patients who had |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td></td>
<td>a baseline evaluation and at least one on-therapy evaluation = 630</td>
</tr>
<tr>
<td></td>
<td>Safety analysis: patients with at least one dose of randomized therapy = 683 631 completed the study</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source:</strong> Bristol-Myers Squibb Pharmaceutical Research Institute</td>
</tr>
<tr>
<td>Lacourciere 1994 [25]</td>
<td><strong>Design:</strong> 12-week double-blind, placebo-controlled, parallel 3 X 4 factorial design study after a 4-week single-blind placebo run-in period. Randomized (methods not described)</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> 240 outpatients of both sexes, aged 18-70 yrs, with sitting DBP between 95 and 110mmHg, on the last visit during the run-in period. On average, the patients were aged in the early fifties and predominantly male.</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> 12 treatment groups (od): Placebo Monotherapy: Niebivolol 1mg (N1); N5; N10; HCTZ 12.5mg (H12.5); H25 Combination: N1H12.5; N1/H25; N5/H12.5; N5/H25; N10/H12.5; N10/H25</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes:</strong> Trough (24hrs post dose) sitting SBP and DBP; HR (no extractable data provided for analysis)</td>
</tr>
<tr>
<td></td>
<td><strong>Notes:</strong> 226/240 patients completed the study. Efficacy analyses versus baseline and placebo were performed after four weeks on double-blind treatment and at the last available visit or end-point. All 240 patients were included. “No significant changes in HR in N1 or H monotherapies and combination groups. N5 and N10 monotherapies and in combination with H induced a significant reduction from baseline in seated HR (range 10.4-12.4bpm and 2.0-11.5bpm respectively)”</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source:</strong> Janssen Research Foundation and Le Centre Hospitalier de l'Universite Laval, Research Centre</td>
</tr>
<tr>
<td>Lacourciere 2005 [26]</td>
<td><strong>Design:</strong> 8 week double-blind, parallel group study after a 2-week placebo run-in period. Randomized by next available sequential number to receive double-blind treatment.</td>
</tr>
<tr>
<td>Study</td>
<td>Study Description</td>
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</table>
| **Participants:** 774 patients with SBP $\geq$160 and $\leq$200 mmHg after washout period. Mean age: 60 years.  
**Interventions:** 3 treatment groups (od):  
Monotherapy: Valsartan 160mg  
Combination: Valsartan 160mg plus Hydrochlorothiazide 12.5mg or 25mg  
Drugs were forced titrated at week 4:  
Group 1: from valsartan 80mg to valsartan 160mg  
Group 2: from valsartan 160mg to valsartan 160mg plus H12.5  
Group 3: from valsartan 160mg to valsartan 160mg plus H25  
**Primary and Secondary Outcomes:** Trough sitting SBP and DBP; WDAEs  
**Notes:** ITT population: 767 patients; 411 (54%) men.  
**Funding Source:** Novartis Pharmaceuticals  
| Lenz 1994 [27] | **Design:** 8 week multicentre, double-blind, forced-titration parallel group study after 4-week placebo-baseline period. Randomized (methods not described). At week 4, doses are doubled. Only data up to 4 weeks are used.  
**Participants:** 368 men and women, at least 18yrs, with supine DBP $\geq$105 mmHg and $\leq$120 mmHg at two consecutive visits at end of placebo phase. 165 (45%) male. 364 (99%) white.  
**Interventions:** 3 treatment groups (od):  
Monotherapy: Quinapril 10mg (Q10); HCTZ 12.5mg (H12.5)  
Combination: Q10/H12.5  
**Primary and Secondary Outcomes:** Trough standing BP; WDAE  
**Notes:** ITT analysis: all patients with data from placebo-baseline period and double-blind phase. Patients with only data within fewer than 19 days are excluded. (n=318)  
346/369 patients completed the study  
All patients included in safety analysis. |
<table>
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<tr>
<th>Study</th>
<th>Study Description</th>
</tr>
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</table>
| **Li 2003 [28]** | **Funding Source**: Parke-Davis GmbH<br>**Design**: 8-week double-blind, parallel-group study after a 2-week single-blind placebo phase. Randomized (methods not described). After 4 weeks, patients with uncontrolled sitting DBP (≥90mmHg) received double doses. Only data up to 4 weeks of treatment were used in this review.  
**Participants**: 179 patients aged 18-65 with sitting DBP 95-115mmHg and sitting SBP <180mmHg after placebo washout. Mean age: 46.6 yrs. 65% male.  
**Interventions**: 2 treatment groups (od):<br>Monotherapy: Losartan 50mg  
Combination: Losartan 50mg plus HCTZ 12.5mg  
**Primary and Secondary Outcomes**: Trough (22-26 hours post dose) sitting SBP and DBP; WDAE  
**Notes**: Efficacy analysis: "all patients treated" approach - i.e. included all patients who received active treatment and who had valid BP measurements at baseline and on treatment. (n=175)  
Safety analysis: (n=179)  
**Funding Source**: Merck & Co Inc. |
| **MacKay 1996 [29, 30]** | **Design**: 12-week double-blind, parallel group placebo-controlled multicenter study after a 4-week single blind placebo run-in. Stratified randomization.  
**Participants**: 703 men and women at least 18 years of age with sitting DBP ≥95mmHg after first 2 weeks of placebo run-in, and sitting DBP of 95 to 115mmHg (not differed by more than 7mmHg) after last 2 weeks of placebo run-in. 420 (60%) male. Mean age: 53 yrs. 86% white, 12% black, 2% other.  
**Interventions**: 5 treatment groups (od):  
placebo  
monotherapy: losartan 50mg (L50), HCTZ 12.5mg (H 12.5)  
combination: L50/H6.25; L50/H12.5 |
<table>
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<tr>
<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td><strong>Primary and Secondary Outcomes</strong>: trough (22-26hr) sitting DBP and SBP; heart rate (data not shown), WDAE</td>
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<tr>
<td><strong>Notes</strong>: 604/703 patients completed the study. Efficacy analysis: included all randomized patients with at least one treatment period measurement (using last observation carried forward). “No clinically significant mean changes from baseline for heart rate in any groups.” Safety analysis: all patients for whom safety data were available</td>
<td></td>
</tr>
<tr>
<td><strong>Funding Source</strong>: Merck Research Laboratories, Clinical Research</td>
<td></td>
</tr>
<tr>
<td>Manning 1996 [31]</td>
<td><strong>Design</strong>: 6-week multicentre, double-blind, placebo-controlled study after a 4-6 week run-in period. After the 6-week treatment, another 4-week treatment followed where patients could be titrated to 2x dosage depending on the response (data not retrieved). Randomized (methods not described).</td>
</tr>
<tr>
<td><strong>Participants</strong>: 63 patients, aged between 18 and 80 years, with supine resting diastolic BP between 95 and 115 mmHg on two occasions and the lower reading within 10% of the higher reading during the run-in period. Mean age: 53.3yrs. 64% male.</td>
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<tr>
<td><strong>Interventions</strong>: 3 treatment groups (od): Monotherapy: Controlled release diltiazem 150mg (D150); Normal release HCTZ 12.5mg (H12.5) Combination: D150/H12.5</td>
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<tr>
<td><strong>Primary and Secondary Outcomes</strong>: Supine SBP and DBP (timing of measurement not reported); HR; WDAE</td>
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<tr>
<td><strong>Notes</strong>: Efficacy Analysis in 61 patients 61/63 patients completed the study</td>
<td></td>
</tr>
<tr>
<td><strong>Funding Source</strong>: Not reported</td>
<td></td>
</tr>
<tr>
<td>McGill 2001 [32, 33]</td>
<td><strong>Design</strong>: 8-week multicenter, double-blind, double-dummy, placebo-controlled, parallel group, 4x5 factorial study after a 4-week, single-blind, placebo run-in</td>
</tr>
</tbody>
</table>
period. Randomization was according to enrollment order and a computer-generated list, and was stratified by race (black/non-black)

Participants: 818 men and women aged between 18 and 80 years with supine DBP between 95-114mmHg during the last 2 weeks of placebo run-in and SBP between 140 and 200mmHg immediately before randomization. Mean supine DBP could not vary by >7mmHg over last 2 weeks of run-in. Mean age: 53 yrs. 60% men. 27.1% black and 72.9% non-black.

Interventions: 4x5 treatment groups (o.d.):
Placebo
Monotherapy: Telmisartan 20mg (T20); T40; T80; T160; HCTZ 6.25mg (H6.25); H12.5; H25
Combination: T20/H6.25; T40/H6.25; T80/H6.25; T160/H6.25; T20/H12.5; T40/H12.5; T80/H12.5; T160/H12.5; T20/H25; T40/H25; T80/H25; T160/H25

Primary and Secondary Outcomes: Trough (24 hours post dose) supine SBP and DBP; HR (no extractable data); WDAE

Notes: Of the 1293 patients screened, 818 were enrolled. 749/818 patients completed the trial.
ITT: randomized patients with >=1 post randomization BP measurement (n=807 patients) (last observation carried forward)
"No significant changes from baseline were seen in supine trough heart rate with any of the active treatments"

Funding Source: Not reported

Merrill 1987 [34] Design: 8-week multiclinic double-blind trial. Randomized (methods not described)

Participants: 207 patients with a sitting DBP of 90-115mmHg after a 4week placebo baseline.
<table>
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<th>Study</th>
<th>Study Description</th>
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<tr>
<td><strong>Interventions</strong>: 5 treatment groups (o.d):</td>
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<tr>
<td></td>
<td>Monotherapy: Lisinopril 20mg (L20); HCTZ 12.5mg (H12.5)</td>
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<tr>
<td></td>
<td>Combination: L20/H6.25; L20/H12.5; L20/H25</td>
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<tr>
<td><strong>Primary and Secondary Outcomes</strong>: Trough SBP and DBP (timing of measurement not reported); WDAE</td>
<td></td>
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<tr>
<td><strong>Notes</strong>: Source: Paper abstract</td>
<td></td>
</tr>
<tr>
<td><strong>Funding Source</strong>: Not reported</td>
<td></td>
</tr>
<tr>
<td>Mersey 1993 [35]</td>
<td><strong>Design</strong>: 8-week double-blind placebo-controlled multicenter study after 4-6 week placebo period. Randomized (methods not described)</td>
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<tr>
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<td><strong>Participants</strong>: 345 white men and women with sitting DBP of 92 to 109 on two occasions during the placebo period. Efficacy data in 322 patients (58% men; mean age: 50.8yrs)</td>
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<tr>
<td></td>
<td><strong>Interventions</strong>: 5 treatment groups (o.d):</td>
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<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td>Monotherapy: Captopril 25mg (C25); HCTZ 12.5mg (H12.5)</td>
</tr>
<tr>
<td></td>
<td>Combination: C25/H12.5; C50/H25</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Trough (24+-3 hrs post dose) sitting SBP and DBP; HR (no extractable data); WDAE</td>
</tr>
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</table>
|               | **Notes**: Efficacy analysis in 322 patients
296/345 patients completed the study
“the only statistically significant change in HR was in C50/H25 group”                                                                                                                                                                                                                                                                                                                                                           |
|               | **Funding Source**: Bristol-Myers Squibb Company                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Meyer 1994 [36] | **Design**: 16-week multicenter trial after 4-week single-blind placebo run-in. Randomized (methods not described)                                                                                                                                                                                                                                                                                                                                                                            |
|               | **Participants**: 205 patients with DBP of 95-115mmHg after placebo run-in. 63% male. Mean age: 51 yrs.                                                                                                                                                                                                                                                                                                                                                                                          |
**Study** | **Study Description**
--- | ---
**Interventions**: 3 treatment groups (od):  
Monotherapy: Trandolapril 2mg (T2); HCTZ 25mg (H25)  
Combination: T2/H25

**Primary and Secondary Outcomes**: Trough (24 hours post-dose) supine SBP and DBP; WDAE (treatment-related only); HR (no quantitative data)

**Notes**: “No clinically significant changes in supine or standing heart rate”  
Efficacy analysis was done in the overall population.

**Funding Source**: Not reported

| Neutel 2007 [37] | **Design**: 12-week double-blind, parallel-group study after a 21-day single-blind placebo wash-out period. Randomized (methods not described)

**Participants**: 538 patients aged 18 years or older with moderate hypertension that at enrolment was either untreated for at least 4 weeks or uncontrolled by monotherapy. Untreated patients were enrolled if seated SBP 160-179mmHg or seated DBP 100-109mmHg. Patients on monotherapy could be enrolled if seated SBP 150-179mmHg or DBP 95-109mmHg. Mean age 55yrs. 292 (55%) male. 84% white and 14% black/African-American. 228 (42.4%) had hyperlipidemia,. 74 (13.8%) had diabetes mellitus.

**Interventions**: 3 treatment groups (od):  
Monotherapy:  
Hydrochlorothiazide - H12.5 for 2 weeks followed by forced titration to H25 for 10 weeks  
Irbesartan - I150 for 2 weeks followed by forced titration to I300 for 10 weeks  
Combination:  
I150/H12.5 for 2 weeks followed by forced titration to I300/H25 for 10 weeks

**Primary and Secondary Outcomes**: Trough sitting SBP and DBP; WDAE

**Notes**: 472 patients (87.7%) completed double-blind treatment.  
Efficacy analyses in all randomized subjects (ITT)
<table>
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<tr>
<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td>Study Description</td>
<td>Safety analyses in all randomized patients who took at least 1 dose of study medication (n=538)</td>
</tr>
<tr>
<td><strong>Funding Source</strong></td>
<td>Bristol-Myers Squibb and Sanofi-Aventis</td>
</tr>
<tr>
<td>Oparil 1980 [38]</td>
<td><strong>Design:</strong> 8-week double-blind study after 6 week placebo period; randomized study (methods not described)</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>97 outpatients, 21-65 yrs, with supine DBP between 100-120 mmHg. Difference between weeks 2 or 4 and week 6 of placebo phase &lt;=10 mmHg. Mean age: 51 yrs. 34 (35%) male; 62 (64%) white</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>3 treatment groups (bid):</td>
</tr>
<tr>
<td></td>
<td>Monotherapy: Timolol maleate 10mg (T10); HCTZ 25mg (H25)</td>
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<td></td>
<td>Combination: T10/H25</td>
</tr>
<tr>
<td><strong>Primary and Secondary Outcomes</strong></td>
<td>Erect SBP and DBP; WDAE; supine HR (only range was given; not extracted for analysis)</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>90/97 patients completed the study</td>
</tr>
<tr>
<td></td>
<td>Efficacy analysis not described (n=78 at week 8)</td>
</tr>
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<td>For HR, &quot;the decrease (bpm) ranged from 16 to 18 in the timolol/HCTZ group, 14 to 17 in the timolol group, and 5 to 6 in the HCTZ group&quot;</td>
</tr>
<tr>
<td><strong>Funding Source</strong></td>
<td>Merck Sharp &amp; Dohme</td>
</tr>
<tr>
<td>Papademetriou 2000 [39]</td>
<td><strong>Design:</strong> 8-week multicenter, double-blind, placebo controlled study after a 4-5 week placebo run-in phase. Randomized (methods not described).</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>275 patients with DBP between 95-114 mmHg on 2 separate occasions during clinic visits. 56% male, 21% black. Mean age: 52 years.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>4 treatment groups (od):</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td>Monotherapy: Hydrochlorothiazide 12.5mg (H12.5); Candesartan 32mg (C32)</td>
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<tr>
<td></td>
<td>Combination: H12.5/C32</td>
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<tr>
<td>Study</td>
<td>Study Description</td>
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</tbody>
</table>
| Papademetriou 2006 [40] | **Primary and Secondary Outcomes**: Trough sitting SBP and DBP; WDAE; HR (no extractable data)  
  **Notes**: “No clinically significant changes in HR”  
  **Funding Source**: Not reported |

**Design**: 8-week multicenter, double-blind, parallel group, unbalanced factorial study after a 4- to 5-week single-blind placebo run-in period. A central, computer-generated randomization schedule using an interactive voice response system was used.  

**Participants**: 1571 patients aged 18 to 80 years with sitting DBP 95 to 114mmHg and SBP <180mmHg after placebo run-in. Mean age: 53 years. About half were men. 26% were African American. 10% had diabetes mellitus type 2.  

**Interventions**: 17 treatment groups (o.d.):  
Placebo  
Monotherapy: ER Metoprolol (M25, M50, M100, M200); Hydrochlorothiazide (H6.25, H12.5, H25)  
Combination: M25/H6.25; M25/H12.5; M50/H6.25; M50/H12.5; M100/H6.25; M100/H12.5; M100/H25; M200/H12.5; M200/H25  
**Primary and Secondary Outcomes**: Trough sitting SBP and DBP; WDAE (not used; only total percentage of WDAE reported); HR (no extractable data)  

**Notes**: Efficacy analyses: ITT on all randomized patients taking at least one dose of study drug, and with at least one post baseline BP.  
2.9% of patients had WDAE. There were no deaths.  
“Heart rate decreased with increasing doses of ER-metoprolol (maximal decrease of 10 beats/min at 200mg) and did so independent of hydrochlorothiazide”  

**Funding Source**: AstraZeneca LP
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<th>Study</th>
<th>Study Description</th>
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</table>
**Participants**: 353 patients aged between 18 and 75 years and a sitting DBP between 95 and 110mmHg placebo wash-out. Mean age: 57 years. 56% male.  
**Interventions**: 10 treatment groups (o.d.):  
Monotherapy: Zofenopril (Z15, Z30, Z60); Hydrochlorothiazide (H12.5, H25)  
Combination: Z15/H12.5; Z30/H12.5; Z60/H12.5; Z15/H25; Z30/H25  
**Primary and Secondary Outcomes**: Trough sitting SBP and DBP; WDAE (numbers of WDAE in each group not reported); HR (no extractable data)  
**Notes**: 330 patients completed the trial.  
Efficacy analyses: ITT - all randomized patients who received at least one dose of the treatment drug and who had at least one visit after baseline (n=353).  
6 (1.7%) patients with WDAE.  
Safety analyses: all randomized patients.  
“No significant differences in heart rate between groups or from baseline”  
**Funding Source**: Menarini Industrie Farmaceutiche Riunite and Istituto Lusofarmaco d'Italia |
| Philipp 1997 [42] | **Design**: 8-week double-blind, factorial design, multicentre study after a 4-week placebo run-in period. Randomized (methods not described)  
**Participants**: 1096/1306 patients aged 18-75 years with sitting diastolic BP of 95-110mmHg. Mean age: 55.1 years.  
**Interventions**: 15 parallel groups (od):  
Placebo  
Candesartan Cilexetil 2, 4, 8 or 16mg,  
HCTZ 12.5 or 25mg  
Combination therapy with both agents at these respective doses |
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<th>Study</th>
<th>Study Description</th>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes:</strong> Sitting SBP and DBP (timing of measurement not reported); HR (data not shown); WDAE (given as percentages; number of WDAE in each group not reported)</td>
</tr>
</tbody>
</table>
|            | **Notes:** ITT efficacy analysis in 1038 patients. 485 (47%) male.  
““No effects on heart rate”  
2.4% of patients withdrew from the study due to adverse occurrences. |
|            | **Funding Source:** Not reported |
| Pool 1987 [43] | **Design:** 12-week multicenter study after a placebo medication for 2-4 weeks.  
Randomized (methods not described). After week 4 or 8, the dosage could be double to achieve the target BP. Therefore, only data up to week 4 will be used in this review.  
**Participants:** 394 patients of either sex, aged >=18 years, with sitting DBP of 90-120mmHg inclusive after placebo period. Women of childbearing potential were actively practicing birth control. 75% male. Mean age: 73 years. 73% white; 21% black.  
**Interventions:** 3 treatment groups (o.d.) in 2:2:1 ratio:  
Monotherapy: lisinopril 20mg (L20); HCTZ 12.5mg (H12.5)  
Combination: L20/H12.5  
Double-dummy technique  
**Primary and Secondary Outcomes:** Sitting SBP and DBP (timing of measurement not reported); HR  
**Notes:** Efficacy analysis: "per-protocol" methods with all completed patients but excluded protocol deviations and dropouts if dropout occurred prior to the time point being analyzed. (n=368)  
"all-patients-treated" method was also used but data not shown.  
**Funding Source:** Not reported |
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</table>
| Pool 1993 [44] | **Design:** 6-week multicenter, double-blind, placebo-controlled, parallel group trial after a 4-6 week single-blind placebo run-in phase. Randomized (methods not described)  

**Participants:** 298 patients, aged 18-70 years, with 2 consecutive weekly mean supine DBP of 95-110mmHg, that varied ≤7mmHg after baseline phase.  

**Interventions:** 4 treatment groups (bid):  
Placebo  
Monotherapy: Diltiazem SR 120mg (D120); HCTZ 12.5mg (H12.5)  
Combination: D120/H12.5  

**Primary and Secondary Outcomes:** Trough (+-2hours prior to the next scheduled dose) standing SBP and DBP; HR (not shown)  

**Notes:** 254/298 patients completed the study. 79% non-black. Mean age 54.4yrs. 66% men.  
Efficacy data set included only participants who were randomized and completed the enter study protocol without being discontinued or having a protocol violation (n=254)  
"no significant changes in supine HR from baseline to end of study for any of the treatment groups"  
"all active treatment were well tolerated, with essentially equivalent rates of drop-outs due to side effects"  

**Funding Source:** Marion Merrell Dow Inc. |
| 1997 [45] | **Design:** 8-week multicenter 4 X 4 factorial, double blind, parallel group trial after a single-blind, placebo lead-in of 4-5 weeks. Randomized (methods not described).  

**Participants:** 550 white, Asian or black outpatients aged 1 to 75 years inclusive with seated DBP >=95mmHg and <=110mmHg at consecutive visits (3rd or 4th weeks, or 4th and 5th weeks) during placebo lead-in. Mean age: 51.5 yrs. 335 (61%) male. 461 (84%) white and 82 (15%) black. |
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<th>Study</th>
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</table>
| **Interventions:** 16 treatment groups (o.d.):  
Placebo  
Monotherapy: Fosinopril 2.5mg (F2.5); F10; F40; HCTZ 5mg (H5); H12.5; H37.5  
Combination: F2.5/H5; F2.5/H12.5; F2.5/H37.5; F10/H5; F10/H12.5; F10/H37.5; F20/H12.5; F40/H5; F40/H12.5; F40/H37.5;  
**Primary and Secondary Outcomes:** Trough (24+-3hrs post dose) sitting SBP and DBP; HR (data not shown); WDAE  
**Notes:** Efficacy analysis: 1) using ITT population: patients having BP data at baseline and at least one follow-up visit and 2) using efficacy population: subset of the ITT population, made up of all patients who did not violate any of the terms in the protocol that might affect efficacy outcome. Only data on ITT population were presented (n=516). 506/550 patients completed the study  
**Funding Source:** Bristol-Myers Squibb Company |
| Pool 2007a [46] | **Design:** 8-week multicenter, double-blind, multifactorial study after a 3- to 4-week single-blind placebo run-in period. Randomization by region was performed by interactive voice response system provider using a validated system that automates the random assignment of treatment groups to randomization numbers. Randomization codes were kept strictly confidential until the database was locked.  
**Participants:** 1123 men and non-pregnant women >= 18 years of age with mean sitting DBP >=95mmHg after a placebo run-in. Patients with mean sitting DBP >=110mmHg or SBP >= 180mmHg were excluded. Mean age 56.1yrs. 56% male. 92% white; 7% African American.  
**Interventions:** 11 treatment arms (o.d.):  
Placebo  
Monotherapy: Aliskiren (A75, 150 or 300mg); Valsartan (V80, 160, 320mg)  
Combination: A75/V80; A150/V160; A300/V320; V160/HCTZ 12.5 |
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<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td><strong>Primary and Secondary Outcomes</strong>: sitting (trough?) SBP and DBP; AEs, WDAE,</td>
<td></td>
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<tr>
<td><strong>Notes</strong>: ITT: all randomized patients with baseline and at least one post-baseline measurement (n=1117)</td>
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<tr>
<td>safety analyses: all randomized patients who received at least one dose of study treatment (n=1123)</td>
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<tr>
<td><strong>Funding Source</strong>: Novartis Pharma AG</td>
<td></td>
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<tr>
<td><strong>Notes</strong>: ITT: Efficacy analyses in all randomized patients who had a baseline and with post-baseline efficacy measurement (n=1329)</td>
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<tr>
<td>Safety analyses: all randomized patients who received trial medication in a double-blind manner.</td>
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<tr>
<td>Sex distribution in baseline characteristics (P=0.025)</td>
<td></td>
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<tr>
<td><strong>Funding Source</strong>: Novartis Pharmaceuticals Corporation</td>
<td></td>
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<td>Study</td>
<td>Study Description</td>
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<tr>
<td>Prisant 2000</td>
<td><strong>Design</strong>: 6-week double-blind, placebo-controlled, parallel-group, multicenter study after a 4-week single-blind placebo treatment. Randomized (methods not described).</td>
</tr>
<tr>
<td></td>
<td><strong>Participants</strong>: 429 men or women aged 18-80 years with supine DBP within the range of 95 to 114mmHg after 3 and 4 weeks of placebo treatment with a difference between measurements of 7mmHg or less.</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions</strong>: 13 treatment groups (od): Placebo Monotherapy: Diltiazem XR (120, 180, 240, or 360mg); Indapamide (1.25 or 2.5mg) Combination: each of the combination of Diltiazem plus indapamide (excluding Diltiazem 360mg)</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Trough (before next morning dose) supine SBP and DBP; WDAE (only total was given; number of WDAE for each group not reported)</td>
</tr>
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<td></td>
<td><strong>Notes</strong>: The variability of indapamide 1.25mg was too large to demonstrate consistent effects and was not discussed in the article. Baseline demographics of all treated patients were similar (n=329): 60% male. Age: 50-54yrs. &quot;no pattern was observed in the rate of discontinuations to adverse events or incidence of adverse events among patients who received any treatment&quot;</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source</strong>: Not reported</td>
</tr>
<tr>
<td>Romero 1995</td>
<td><strong>Design</strong>: 8-week multicenter, double-blind, active-controlled parallel study after 2-4 week placebo phase; randomized (method not described)</td>
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<tr>
<td></td>
<td><strong>Participants</strong>: 323 men and women, &gt;=18yrs, with supine diastolic BP of &gt;=105 and &lt;=120 mm Hg at 2 consecutive visits during the placebo period. Mean age: 53yrs. 9 black, 1 Arabian, 313 white. 57% male.</td>
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<tr>
<td></td>
<td><strong>Interventions</strong>: 3 parallel treatment groups (o.d.) with placebo matching drugs: monotherapy: Quinapril 20mg (Q20); HCTZ 12.5mg (H12.5) combination: Q20/H12.5</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Trough (24hr) supine DBP and SBP; HR (no quantitative data); WDAE</td>
</tr>
<tr>
<td></td>
<td><strong>Notes</strong>: Efficacy analysis using evaluable data analysis: all patients without protocol deviations with &gt;= 26 days of double-blind treatment, with the data of the last visit as endpoint = 291 (used)</td>
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<tr>
<td></td>
<td>“Heart rate was not significantly modified in any of the groups”</td>
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<tr>
<td></td>
<td><strong>Funding Source</strong>: Parke Davis GmbH</td>
</tr>
<tr>
<td>Rosenthal 1990 [50]</td>
<td><strong>Design</strong>: 4-week double-blind four-center study after a 2-week baseline placebo period. Randomized (methods not described). After 4 weeks, normotensives with DBP of 90-95mmHg continued the same dosage for 4 more weeks; the others took double dosages (data were not used in this review)</td>
</tr>
<tr>
<td></td>
<td><strong>Participants</strong>: 81 patients, aged 24 to 70, with supine diastolic BP of 100-120 after placebo period. Mean age: 52 years. 58 (72%) men.</td>
</tr>
</tbody>
</table>
|               | **Interventions**: 3 treatment groups (od):  
|               | Monotherapy: Enalapril 20mg (E20); Hydrochlorothiazide 12.5 (H12.5)  
|               | Combination: E20/H12.5                                                                                                                                                                                                                                       |
|               | **Primary and Secondary Outcomes**: Trough supine SBP and DBP                                                                                                                                                                                                       |
|               | **Notes**: 69/81 patients completed the 8-week study.                                                                                                                                                                                                               |
|               | **Funding Source**: Not reported                                                                                                                                                                                                                                 |
| Safar 1973 [51, 52] | **Design**: 45 days double-blind study after a 15 days placebo period.  
<p>|               | Randomized (methods not described).                                                                                                                                                                                                                              |
|               | <strong>Participants</strong>: 30 men with DBP &gt;=100mmHg. Mean age: 40years.                                                                                                                                                                                                     |</p>
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<tr>
<th>Study</th>
<th>Study Description</th>
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<tbody>
<tr>
<td></td>
<td><strong>Interventions</strong>: 2 treatment groups:</td>
</tr>
<tr>
<td></td>
<td>Monotherapy: Pindolol 5mg tid</td>
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<tr>
<td></td>
<td>Combination: Pindolol 5mg tid plus Clopamide 10mg od</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Standing SBP and DBP and HR (timing of measurement not reported); WDAE</td>
</tr>
<tr>
<td></td>
<td><strong>Notes</strong>: Language: French</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source</strong>: Not reported</td>
</tr>
<tr>
<td>Safar 1994 [53]</td>
<td><strong>Design</strong>: 8-week double-blind study after 4-week single-blind placebo run-in period. (Randomized: methods not described).</td>
</tr>
<tr>
<td></td>
<td><strong>Participants</strong>: 465 patients, 19-72yrs, with supine DBP between 95 and 114mmHg.</td>
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<td></td>
<td><strong>Interventions</strong>: 6 treatment groups (od)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
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<tr>
<td></td>
<td>Monotherapy: Perindopril 4mg (P4); Indapamide 1.25mg (I1.25)</td>
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<tr>
<td></td>
<td>Combination: P4/I0.625; P4/I1.25; P4/I2.5</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Supine DBP (timing of measurement not reported); WDAEs (number of WDAE in each group not reported)</td>
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<td><strong>Notes</strong>: Source: Poster</td>
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<td>In total, 25 patients discontinued from the study (14 due to AEs)</td>
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<tr>
<td></td>
<td>Safety data: ITT analysis.</td>
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<tr>
<td></td>
<td><strong>Funding Source</strong>: Not reported</td>
</tr>
<tr>
<td>Saruta 2007 [54]</td>
<td><strong>Design</strong>: 8-week double-blind, parallel group study after 4 to 6 weeks of placebo run-in period. Randomized (methods not described).</td>
</tr>
<tr>
<td></td>
<td><strong>Participants</strong>: 961 Japanese patients between 25 and 74 years of age with mean trough sitting DBP of 95 to 115mmHg and SBP &lt;210mmHg at each visit</td>
</tr>
<tr>
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<td>throughout the placebo run-in period up to the day of randomization.</td>
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<td></td>
<td><strong>Interventions:</strong> 6 treatment arms (o.d.):</td>
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<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Monotherapy: Losartan 50mg (L50); hydrochlorothiazide 12.5mg (H12.5)</td>
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<tr>
<td></td>
<td>Combination: L25/H6.25; L50/H6.25; L50/H12.5</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes:</strong> Trough sitting SBP and DBP and HR; WDAE</td>
</tr>
<tr>
<td></td>
<td><strong>Notes:</strong> Efficacy analyses in 942 patients who took at least one dose of study medication and have data of trough DBP post-randomization Safety analyses: patients who had taken the study medication at least once (n=954)</td>
</tr>
<tr>
<td>Saul 1995</td>
<td><strong>Design:</strong> 8-week double-blind treatment following a 4-week, single-blind, placebo run-in period. Randomized (methods not described).</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> 256 patients, aged 18 to 80 years, with sitting DBP of 100-114 mmHg (inclusive) during placebo run-in. 142 (55%) men. Mean age: 57.6yrs.</td>
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<tr>
<td></td>
<td><strong>Interventions:</strong> 3 treatment groups (od):</td>
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<tr>
<td></td>
<td>Monotherapy: Lisinopril 10mg (L10); HCTZ 25mg (H25)</td>
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<tr>
<td></td>
<td>Combination: L10/H25</td>
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<td>Ratio of 2:1:1 for L/H:L:H</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes:</strong> Trough (22-26 hours post-dose) sitting SBP and DBP; HR (no quantitative data); WDAE</td>
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<td><strong>Notes:</strong> Efficacy analysis: Completed patients' analysis which included all randomized patients who completed the study. As no patients violated the study criteria, this is also an ITT analysis. “Only small mean changes in heart rate from baseline and there were no significant treatment differences”</td>
</tr>
<tr>
<td></td>
<td><strong>Funding Source:</strong> Banyu Pharmaceutical Co. Ltd.</td>
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Funding Source: Not reported
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</table>
| Schoenberger 1986 [56] | **Design:** 16-week double-blind multicenter study after a 4-6 week placebo lead-in period. Randomized (methods not described). Captopril doses were double at the end of first 4 weeks of active treatment. Only data up to 4 weeks were used in this review.  
  
  **Participants:** 382 Caucasian or Hispanic patients, aged ≥18 yrs, with DBP 92-110 mmHg on the last two visits of placebo period. Approximately 65% male. Mean age: 52 yrs.  
  
  **Interventions:** 4 treatment groups:  
  - Placebo bid  
  - Monotherapy: Captopril 50mg (C50) o.d.; C50 bid  
  - Combination: C50 o.d. plus HCTZ 25mg o.d.  
  
  **Primary and Secondary Outcomes:** Trough (24+-3 hours post dose) sitting SBP and DBP  
  
  **Notes:** Efficacy analysis in 358 patients.  
  
  **Funding Source:** Not reported                                                                                                                                          |
| Thijs 1995 [57] | **Design:** 4-week double-blind multicenter trial after a 2-4 week single-blind placebo run-in phase. Randomized (methods not described). Treatment was discontinued if DBP <80 or >115 mmHg.  
  
  **Participants:** 611 men and women aged 21-70 years with supine DBP averaged 100-114 mmHg. Supine SBP <220 mmHg. 51% men. Mean age: 55 years.  
  
  **Interventions:** 3 parallel groups (o.d.):  
  - Monotherapy: Ramipril 5mg (R5); Piretanide 6mg (P6)  
  - Combination: R5/P6  
  
  **Primary and Secondary Outcomes:** Trough (24 hours post-dose) standing SBP and DBP; WDAE                                                                                                                                                                                                 |
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<th>Study Description</th>
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</table>
| **Vaicaitis 1980 [58]** | **Design:** 8-week multiclinic, double-blind study after 6 week baseline phase with placebo; randomized (method not described)  
**Participants:** 27 outpatients 21 to 65 years of age with supine diastolic BP between 100 and 120 mm Hg at end of baseline phase. Difference between week 2 or 4 and week 6 $\leq 10$ mm Hg. Sitting systolic BP $< 160$ mm Hg. Heart rate $\geq 56$ beats/min. Mean age: 54 yrs. 17 (63%) male.  
**Interventions:** 3 treatment groups (one tablet bid):  
Monotherapy: Timolol maleate 10mg (T10); HCTZ 25mg (H25)  
Combination: T10/H25  
**Primary and Secondary Outcomes:** Erect SBP and DBP (timing of measurement not reported); supine pulse rate; WDAE  
**Notes:** Efficacy analysis not described (n=22)  
**Funding Source:** Merck Sharp & Dohme |
| **Villamil 2007 [59]** | **Design:** 8-week, multicenter, double-blind, multifactorial study trial after a 2-week single-blind placebo run-in period. Randomized (methods not described)  
**Participants:** 2776 patients $\geq 18$ years with mean sitting DBP $\geq 95$ mmHg after placebo run-in. Patients with mean DBP $\geq 110$ mmHg and/or SBP $\geq 180$ mmHg were excluded. Mean age: 55 yrs. 55% male. 85% caucasian; 5% blacks.  
**Interventions:** 15 treatment groups (o.d.):  
placebo  
Monotherapy: Aliskiren (A75, A150 or A300mg); Hydrochlorothiazide (H6.25, H12.5 or H25mg)  
**Notes:** Efficacy analysis not described (n=22)  
**Funding Source:** Merck Sharp & Dohme |
<table>
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<tr>
<th>Study</th>
<th>Study Description</th>
<th>Primary and Secondary Outcomes</th>
<th>Notes</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Manteuffel 1995</td>
<td>Combination: A75/H6.25, A75/H12.5, A75/H25, A150/H6.25, A150/H12.5, A150/H25, A300/H12.5, A300/H25</td>
<td>Trough sitting SBP and DBP; WDAE</td>
<td>ITT: all randomized patients with a baseline measurement and at least one post-baseline measurement = 2752 patients; Safety analyses: on all patients who received at least one dose of double-blind study medication = 2762 patients</td>
<td>Not reported</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Trough sitting SBP and DBP; WDAE</td>
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<td><strong>Notes</strong>: ITT: all randomized patients with a baseline measurement and at least one post-baseline measurement = 2752 patients</td>
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<tr>
<td></td>
<td>Safety analyses: on all patients who received at least one dose of double-blind study medication = 2762 patients</td>
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<tr>
<td></td>
<td><strong>Funding Source</strong>: Not reported</td>
<td></td>
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<tr>
<td>Weinberger 1982 [61]</td>
<td><strong>Design</strong>: 6 week double-blind parallel group study after a 4 week placebo washout period. Block randomization was used.</td>
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<tr>
<td></td>
<td><strong>Participants</strong>: 173 patients with DBP of at least 100mgHg and not more than 114mmHg after placebo run-in.</td>
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<tr>
<td></td>
<td><strong>Interventions</strong>: 4 treatment groups (od): Placebo Monotherapy: Verapamil SR 240mg od (V240); Hydrochlorothiazide 12.5mg od (H12.5)</td>
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<td></td>
<td>Combination: V240/H12.5</td>
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<tr>
<td></td>
<td><strong>Primary and Secondary Outcomes</strong>: Seating SBP and DBP (timing of measurement not reported)</td>
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<td><strong>Notes</strong>: Language: German</td>
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<tr>
<td></td>
<td><strong>Funding Source</strong>: Not reported</td>
<td></td>
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</tbody>
</table>
Study | Study Description
---|---
**Interventions**: 3 treatment groups (tid):
Monotherapy: Captopril 25mg (C25); HCTZ 15mg (H15)
Combination: C25/H15

**Primary and Secondary Outcomes**: Supine SBP and DBP (examined 3-8 hours after the last dose of drug); HR (no extractable data for analysis); WDAE

**Notes**: 198/207 patients completed the study.
"Heart rate, both supine and standing, increased slightly (1.4-4.7%) but significantly in both groups receiving H but not the group receiving C alone, where slight (-1.7%-0.7%) but non-significant decreases in heart rate were observed"

**Funding Source**: Not reported

---

Weir 1992 [62] | **Design**: 12-week double-blind, placebo controlled, multicentre study after a 4-6 week single-blind placebo run-in period. The 12 week period consists of three 4-week evaluation period with increasing fixed dose at each period.
Randomized study (methods not described). Data on the first 4-week evaluation period was used in this review.

**Participants**: 298 volunteers between 18 and 70 yrs of age with supine DBP >=95 and <=110 mmHg. Women of childbearing potential were excluded.

**Interventions**: 4 treatment groups (bid):
Placebo
Monotherapy: Diltiazem SR 60mg (D60); HCTZ 6.25mg (H6.25)
Combination: D60/H6.25

**Primary and Secondary Outcomes**: Trough (12+-2hrs post dose) supine SBP and DBP; supine HR (no quantitative data); WDAE

**Notes**: Efficacy analysis: patients who completed a 4-week evaluation period without protocol violations (used) with n = 274 for period 1 (65%male; 86%non-black; mean age = 53.5 yrs)
14 patients discontinued period 1.
**Study** | **Study Description**
---|---
| “No significant differences between groups in HR in period 1”
| **Funding Source**: Marion Merrell Dow Inc.

Yodfat 1994 [63]

| **Design**: 4-week parallel-group placebo-controlled multicentre study after 4-week single-blind placebo period. Randomized (methods not described). Efficacy data up to 4 weeks of treatment were recorded.
| **Participants**: 377 patients of both sexes, between 20 and 68 yrs, with average sitting DBP >100mmHg and those who demonstrated at least 80% compliance after placebo period. 244 (65%) men. Mean age: 53 yrs.
| **Interventions**: 8 treatment groups (o.d.):
  - Placebo
  - Monotherapy: Cilazapril 2.5mg (C2.5); C5; HCTZ 12.5mg (H12.5); H25
  - Combination: C1.25/H6.25; C2.5/H12.5; C5/H25
| **Primary and Secondary Outcomes**: Trough (22-24 hours post dose) sitting DBP; WDAE (number of WDAE for each group not reported)
| **Notes**: 363/377 patients completed the study
  - Only efficacy data up to 4 weeks of treatment were recorded.
  - ITT analysis: number of total patients is not explicitly reported. Assume 'N' for trough BP analysis is same as 'N' in Table 2 which report 'n' patients with normalized BP. (N=373)
| **Funding Source**: Not reported

### 3.1.2 Characteristics of excluded studies

Forty-four of the studies that met the preliminary inclusion criteria were excluded from this review. A majority of the excluded studies were crossover trials in which pre-crossover data were not provided.

The reasons for exclusion of each trial are provided in Table 3.2.
Table 3.2: Reasons for exclusion of trials that met inclusion criteria for this review

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal 1979 [64]</td>
<td>Crossover trial with no pre-crossover data for first 4 or 6 weeks of treatment (Propranolol 80mg bid vs bendrofluazide 2.5mg bid or their combination)</td>
</tr>
<tr>
<td>Agrawal 1987 [65]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (propanolol 80mg od vs bendrofluazide 2.5mg od vs their combination)</td>
</tr>
<tr>
<td>Bateman 1979 [66]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (atenolol 100mg od vs chlorthalidone 25mg od vs their combination vs placebo)</td>
</tr>
<tr>
<td>Bauer 1984 [67, 68]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment. 8 week treatment but titration in non-responders after 4 week treatment. (Enalapril 10mg bid vs Hydrochlorothiazide 25mg bid vs their combination)</td>
</tr>
<tr>
<td>Bertrand 1982 [69]</td>
<td>Chlortalidone given 3 times per week only.</td>
</tr>
<tr>
<td>Boike 1982 [70]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Atenolol 100mg od vs chlorthalidone 25mg od vs their combination vs placebo)</td>
</tr>
<tr>
<td>Bolzano 1984 [71]</td>
<td>Parallel group trial with 8-week treatment period. Hydrochlorothiazide was co-administered with amiloride. (Methyldopa 250mg (M250) vs Hydrochlorothiazide 25mg plus Amiloride 5mg (H25/A5) vs their combination)</td>
</tr>
<tr>
<td>Cajochen 1984 [72]</td>
<td>Crossover trial with BP data for the first 4 weeks of treatment. Number of patients per treatment arm for the first phase of study not mentioned. (Atenolol 100mg od vs Chlorthalidone 50mg od vs their combination)</td>
</tr>
<tr>
<td>Canter 1994 [73]</td>
<td>Parallel group trial with 8-week treatment period. Number of patients per treatment arm not reported (16 parallel arms: placebo; Quinapril 2.5, 10, 40mm/day; Hydrochlorothiazide 6.25, 12.5, 25mg/day; all possible combinations).</td>
</tr>
<tr>
<td>Chalmers 1982 [74]</td>
<td>Crossover trial with no pre-crossover data for first 8 weeks of treatment. (Indapamide 2.5mg od vs Pindolol 10mg od vs their combination vs placebo)</td>
</tr>
<tr>
<td>Chalmers 1986 [75]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Enalapril 10mg bid vs Hydrochlorothiazide 25mg bid vs their combination vs placebo)</td>
</tr>
<tr>
<td>Chrysant 1992 [76]</td>
<td>Parallel group trial with 4-week treatment period. Hydrochlorothiazide was co-administered with triamterene. (Atenolol 25mg vs HCTZ 25mg plus triamterene 50mg vs their combination)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Crowe 1987 [77]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Enalapril 10mg bid vs Hydrochlorothiazide 25mg bid vs their combination vs placebo)</td>
</tr>
<tr>
<td>De Divitiis 1981 [78]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Atenolol 100mg od vs chlorthalidone 50mg od vs their combination vs chlorthalidone 50mg od plus reserpine 0.25mg od)</td>
</tr>
<tr>
<td>De Divitiis 1983 [79]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (indapamide 2.5mg od vs atenolol 100mg vs their combination)</td>
</tr>
<tr>
<td>Durel 1992 [80]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Atenolol 100mg od vs Chlorthalidone 50mg od vs their combination)</td>
</tr>
<tr>
<td>Erwteman 1984 [81]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (chlorthalidone 25mg od vs metoprolol 200mg od vs their combination)</td>
</tr>
<tr>
<td>Fernandez 1980 [82]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (alpha-methyldopa 750mg/day vs chlorothiazide 340mg/day vs their combination vs placebo)</td>
</tr>
<tr>
<td>Forette 1979 [83]</td>
<td>Crossover trial with no pre-crossover data for first 8 weeks of treatment. Clorexolone administered with canrenone. (acebutolol 400mg/day vs clorexolone 3mg/day+canrenone 25mg/day vs their combination).</td>
</tr>
<tr>
<td>Frishman 1987 [84]</td>
<td>Parallel group trial with 48 week treatment period, titration based on response starting at week 4. Pre-titration data not reported. (enalapril 10mg bid vs hydrochlorothiazide 25mg bid vs combination)</td>
</tr>
<tr>
<td>Hart 1985 [85]</td>
<td>Parallel group trial with 4-week treatment period. Hydrochlorothiazide was co-administered with triamterene. (Atenolol 100mg vs HCTZ 25mg plus Triamterene 50mg vs their combination)</td>
</tr>
<tr>
<td>Hunter 1999 [86]</td>
<td>Crossover trial with no pre-crossover data for first 12 weeks of treatment (captopril 50mg bid vs bendrofluazide 2.5mg od vs their combination)</td>
</tr>
<tr>
<td>Jaattela 1979 [87]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Propanolol 80mg bid vs bendrofluazide 2.5mbid vs their combination)</td>
</tr>
<tr>
<td>Jackson 1986 [88]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment. However, HCTZ was co-administered with amiloride. (Atenolol 50mg vs HCTZ 25mg/amiloride 2.5mg od and their combination)</td>
</tr>
<tr>
<td>Khalil 1982 [89]</td>
<td>Crossover trial with pre-crossover data for the first 6 weeks of treatment. However, HCTZ was co-administered with amiloride. (Acebutolol 400mg vs Acebutolol 400mg plus HCTZ 50mg plus Amiloride 5mg)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Description</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kieso 1983</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Metoprolol 200mg od vs Metoprolol 200mg/chlorthalidone 25mg od)</td>
</tr>
<tr>
<td>Kubik 1979</td>
<td>Crossover trial with pre-crossover data for first 8 weeks of treatment. However, number of patients in each group not reported. [Metoprolol 100mg bid (M100) vs M100 bid plus 2 x chlorthalidone-K 25mg od (Chlorthalidone-K tablets each containing 6.7mmol potassium)]</td>
</tr>
<tr>
<td>Lang 1991</td>
<td>Parallel group with 8 week treatment. Number of patients per treatment arm for analysis not included. (Lisinopril 10mg od vs hydrochlorothiazide 12.5mg od vs their combination)</td>
</tr>
<tr>
<td>Lechi 1982</td>
<td>Crossover trial with no pre-crossover data for first 3 weeks of treatment (Labetalol 300mg od vs chlorthalidone 30mg od vs their combination vs placebo)</td>
</tr>
<tr>
<td>Leonetti 1986</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment. (Atenolol 50mg od vs Chlorthalidone 12.5mg od vs their combination)</td>
</tr>
<tr>
<td>Magee 1986</td>
<td>Crossover trial with no pre-crossover data for first 3 weeks of treatment (Nadolol 80mg od and the combination of Nadolol 80mg od with hydrochlorothiazide 12.5, 25 or 50mg od)</td>
</tr>
<tr>
<td>Mehta 1988</td>
<td>Parallel group trial with 24 week treatment period, titration based on response starting at week 4. Pre-titration data not reported (Lisinopril 20mg od vs Lisinopril 20mg/Hydrochlorothiazide 12.5mg od)</td>
</tr>
<tr>
<td>Middlemost 94</td>
<td>Parallel group trial with 8 week treatment period. Only ABPM data given. (Enalapril 20mg od vs enalapril 20mg plus hydrochlorothiazide 12.5mg od)</td>
</tr>
<tr>
<td>Moncloa 1980</td>
<td>Parallel group treatment with 4 week treatment period. Hydrochlorothiazide was co-administered with amiloride. (Methyldopa 250mg bid vs HCTZ 25mg/Amlorilde 2.5mg bid vs their combination)</td>
</tr>
<tr>
<td>Muiesan 1976</td>
<td>Parallel group treatment with 6 week treatment period. Hydrochlorothiazide was co-administered with amiloride. (Timolol 10mg bid vs HCTZ/Amloride 25/2.5mg bid vs their combination)</td>
</tr>
<tr>
<td>Petrie 1975</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Atenolol 100 bid vs bendrofluazide 2.5mg bid vs their combination)</td>
</tr>
<tr>
<td>Ricciardelli 85</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (atenolol 100mg od vs chlorthalidone 25mg plus atenolol 100mg od)</td>
</tr>
<tr>
<td>Rosenthal 1989</td>
<td>Parallel group trial after a 3 week treatment period. Hydrochlorothiazide was co-administered with triamterene. [Verapamil 80mg or 160mg vs</td>
</tr>
<tr>
<td>Study</td>
<td>Study Description</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Triamterene 25mg/HCTZ 12.5mg vs Triamterene 50mg/HCTZ 25mg vs all possible combinations</td>
</tr>
<tr>
<td>Salako 1990 [103]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Atenolol 100mg od vs Chlorthalidone 25mg od vs their combination)</td>
</tr>
<tr>
<td>Salvetti 1989 [104, 105]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Nifedipine 20mg bid vs chlorthalidone 25mg od vs their combination)</td>
</tr>
<tr>
<td>Scholze 1993 [106]</td>
<td>Parallel group trial with 6 weeks treatment period. Number of patient per treatment arm is not reported (placebo vs ramipril 2.5, 5 or 10mg vs HCTZ 12.5 or 25mg vs all possible combinations)</td>
</tr>
<tr>
<td>VACSGAA 1977 [107]</td>
<td>Parallel group with 6 months treatment, titration based on response starting at week 4. Pre-titration data not reported. (Propanolol 40mg tid vs Propanolol in combination with hydrochlorothiazide 35mg or hydralazine 35mg tid vs the combination of 3 drugs)</td>
</tr>
<tr>
<td>Van Staden 19832 [108]</td>
<td>Crossover trial with no pre-crossover data for first 4 weeks of treatment (Propanolol 80mg bid vs Bendrofluazide 2.5mg bid vs their combination)</td>
</tr>
<tr>
<td>Weinberger 1983 [109]</td>
<td>Study B: Parallel group with 12 week treatment period. BP measurements at 3-8hrs after the last drug dose. No properly defined &quot;peak&quot; or &quot;trough&quot; BP measurement. (captopril 52mg bid vs hydrochlorothiazide 25mg bid vs their combination vs placebo)</td>
</tr>
</tbody>
</table>

### 3.2 Imputation of missing variance data

The weighted mean standard deviation (SD) of both SBP and DBP changes were calculated from studies that provided the SD of SBP and DBP changes, respectively. Thirty-two (57%) of the included studies reported the SD of SBP change and thirty-four (61%) included studies reported the SD of DBP change. Eleven studies included in the other three reviews mentioned previously [110-119] also provided the SD of the changes in SBP and DBP. The values from all these studies were pooled in order to calculate the weighted mean estimates of the SD of the change in SBP and DBP for the combination and monotherapy groups. This was based on the assumption that the effect on BP variability is similar across drug classes. Eight studies [14, 16, 17, 23, 31, 111, 112, 116]
were ultimately excluded from the calculation because their SD values were not within three standard deviations of the estimated weighted mean SD of SBP change. For the same reason, five studies [14, 25, 17, 111, 112] were excluded from the calculation of the weighted mean SD of DBP change. After these adjustments, the weighted mean SD of SBP and DBP change values for the combination group were 13.2 (SD 1.5) mmHg and 8.1 (SD 0.8) mmHg, respectively. For the monotherapy group, the weighted mean SD of SBP and DBP change values were 13.6 (SD 1.8) mmHg and 8.3 (SD 1.1) mmHg, respectively. There were no statistically significant differences in the SD of SBP change or the SD of DBP change between the combination and monotherapy groups. These values were used according to the imputation hierarchy for trials that did not report the SD of the BP change value and in the nine included trials that reported outlier SD of the BP change values. The SD of BP change was imputed for 32/56 (57%) of the included studies. Of these studies, 4 (7%) were imputed using the SD of baseline SBP, 2 (4%) imputed using the SD of endpoint SBP, 5 (9%) imputed using the SD of endpoint DBP, 21 (38%) imputed using the weighted mean SD of SBP change from other trials, and 24 (43%) using the weighted mean SD of DBP change from other trials.

### 3.3 Pooling of trials

The diuretics were classified into two groups: 1) loop diuretics; and 2) thiazide and thiazide-like diuretics. The thiazide group was analyzed as a sub-class by pooling all trials that reported trough BP measurements. The loop diuretic group was analyzed separately. The doses of the individual diuretics were categorized as proportions of the manufacturer’s recommended starting dose (Table 3.3). This assumes that the starting dose recommended is effective in reducing BP and that all starting doses have a similar
BP lowering efficacy. In the case where a range of starting doses is recommended by the manufacturer, the lowest dose is considered to be the starting dose (1x).

### Table 3.3 : Starting doses of diuretics analyzed in the review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of Diuretic</th>
<th>Starting dose/day for hypertension</th>
<th>Available in Canada?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>Loop</td>
<td>40-80mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>Piretanide</td>
<td>Loop</td>
<td>6-12mg/day</td>
<td>No</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Thiazide</td>
<td>12.5mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Thiazide</td>
<td>1.25mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Thiazide</td>
<td>12.5mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>Clopamide</td>
<td>Thiazide</td>
<td>5-10mg/day</td>
<td>No</td>
</tr>
</tbody>
</table>

### 3.4 Blood pressure lowering efficacy

The additional BP lowering efficacy of adding a diuretic as second-line therapy to a non-diuretic (“other”) antihypertensive drug is summarized below. The outcome assessed is the difference in BP reduction between the combination (thiazide + other drug) and monotherapy (other drug alone) groups in parallel, double-blind RCTs. Using this approach, the difference is specified as the additional BP reduction induced by adding a diuretic as the second drug.

#### 3.4.1 Thiazide plus other drug vs other drug alone

By comparing the difference in BP reduction between the combination (a thiazide + 1 other drug) and monotherapy (placebo or no treatment + 1 other drug) groups, the additional BP reduction resulting from adding a thiazide as the second drug was estimated.

#### 3.4.1.1 Thiazide plus ACEI vs ACEI alone

Twenty-four included studies assessed the BP lowering efficacy of thiazide plus ACEI combination and ACEI alone. DBP data, which was the primary outcome assessed in all these studies, was provided in all 24 studies, whereas SBP data was provided in only 20 of these studies. HCTZ was the thiazide that was given in all except one study
which assessed indapamide at 0.625mg/day to 2.5mg/day. Although the dose of HCTZ was studied over a wide range (5mg/day to 45mg/day), a majority of the trials evaluated doses of 12.5mg/day and 25mg/day, which correspond to 1x and 2x the manufacturer’s recommended starting dose. In these studies, the drugs were given once daily except for one trial [109] in which the drugs were given three times daily (TID).

Table 3.4: Additional BP reduction by adding a thiazide to ACEI. Fixed effect model (95%CI).

<table>
<thead>
<tr>
<th>Dose of Thiazide in multiples of starting dose</th>
<th># of studies (SBP/DBP)</th>
<th>Total # of patients in combination group (SBP/DBP)</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4x</td>
<td>1/1</td>
<td>93/93</td>
<td>-4.8 (-9.4, -0.2)</td>
<td>-0.8 (-3.2, +1.6)</td>
</tr>
<tr>
<td>0.5x</td>
<td>1/3</td>
<td>42/156</td>
<td>-4.9 (-10.8, +1)</td>
<td>-1.4 (-3.3, +0.4)</td>
</tr>
<tr>
<td>1x</td>
<td>14/17</td>
<td>1112/1274</td>
<td>-5.2 (-6.3, -4.1)</td>
<td>-3.1 (-3.7, -2.5)</td>
</tr>
<tr>
<td>2x</td>
<td>7/11</td>
<td>433/680</td>
<td>-7.5 (-9.4, -5.7)</td>
<td>-3.8 (-4.7, -2.9)</td>
</tr>
<tr>
<td>3x</td>
<td>1/1</td>
<td>92/92</td>
<td>-9.0 (-13.6, -4.4)</td>
<td>-3.5 (-5.9, -1.1)</td>
</tr>
<tr>
<td>3.6x</td>
<td>1/1</td>
<td>62/62</td>
<td>-18.5 (-23.1, -13.9)</td>
<td>-9.2 (-12.0, -6.4)</td>
</tr>
</tbody>
</table>

Two studies provided SBP data for the addition of a thiazide ≤0.5x to an ACEI and the pooled result showed an additional reduction of -4.8 (95% CI -8.4, -1.2) mmHg. There were 4 studies with DBP data that showed the average additional effect on DBP reduction was not statistically significant [-1.2 (95% CI -2.7, +0.3) mmHg].

The combination of thiazide plus ACEI was superior to ACEI alone in lowering both mean SBP and DBP when the dose of thiazide was 1x or greater the manufacturer's recommended starting dose (see Table 3.4). Based on an indirect comparison, the additional SBP reduction achieved by thiazides 2x was statistically greater than by thiazides 1x. However, when 3 of the studies (19, 20, 23) that were judged to have a high risk of incomplete outcome data bias were removed, the difference was no longer statistically significant. A direct comparison of the 2 doses was performed with 3 studies [11, 41, 63] which included HCTZ at both 12.5mg/day and 25mg/day. From the pooled
analysis of these 3 trials, adding HCTZ at 25mg/day also did not show a statistically significant difference in the magnitude of BP reduction compared to adding HCTZ 12.5mg/day \[SBP -1.6 (95\% CI -4.3, +1.2) \text{ mmHg}; DBP -1.1 (95\% CI (-2.4, +0.3) \text{ mmHg})\].

There is only one study assessing thiazide 3x \[45\]. Based on the available evidence, the magnitude of additional reduction achieved with this dose was not significantly greater than those achieved with HCTZ 12.5mg/day or HCTZ 25mg/day. There is also only one study assessing thiazide 3.6x \[61\]. In this study, HCTZ was given at 15mg TID (45mg total daily dose). The addition of HCTZ 15mg TID resulted in a further SBP and DBP reduction that were statistically greater than those achieved with HCTZ at lower doses (see Table 3.4). The data showed that there is a possibility of greater BP reduction with higher HCTZ doses and with TID dosing. However, more studies are needed before conclusions can be made about thiazide doses greater than 2x the starting dose and different dosing schedules.

A sensitivity analysis, where trials that measured BP in standing or supine positions were removed, was performed and showed that our effect estimate was not affected by the position of BP measurement. Removing the single study that assessed indapamide \[53\] in sensitivity analysis also did not statistically change the overall result. BP was measured before the next dosing schedule in all but four studies \[23,43,53,61\] which did not mention the timing of BP measurement. Removing these 4 studies in sensitivity analysis also did not statistically change the BP lowering effect size.

Eight of the 24 included studies were industry sponsored; the other 16 trials did not report funding sources. Therefore, it was not possible to investigate if funding source
affected the results. The mean age of patients in the included studies ranged from 47-58 years and only one study had a study population of mean age >70 years [20]. A subgroup analysis based on age and gender was not performed due to insufficient data.

### 3.4.1.2 Thiazide plus ARB vs ARB alone

Thirteen studies assessed the combination of thiazides plus ARB and ARB alone. HCTZ administered once daily was the only thiazide studied in all 13 trials. Addition of HCTZ (6.25mg/day to 25mg/day) to an ARB significantly reduced both SBP and DBP (Table 3.5).

**Table 3.5 : Additional BP reduction by adding a thiazide to ARB. Fixed effect model (95%CI).**

<table>
<thead>
<tr>
<th>Dose of Thiazide in multiples of starting dose</th>
<th># of studies</th>
<th>Total # of patients in combination group</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5x</td>
<td>4</td>
<td>511</td>
<td>-3.4 (-4.9, -1.8)</td>
<td>-1.6 (-2.5, -0.7)</td>
</tr>
<tr>
<td>1x</td>
<td>12</td>
<td>1911</td>
<td>-7.1 (-8.0, -6.3)</td>
<td>-3.3 (-3.8, -2.8)</td>
</tr>
<tr>
<td>2x</td>
<td>8</td>
<td>1557</td>
<td>-8.4 (-9.4, -7.5)</td>
<td>-4.2 (-4.8, -3.6)</td>
</tr>
</tbody>
</table>

A dose-response was observed, with a statistically significantly greater reduction in BP with the addition of HCTZ 12.5mg/day as compared to HCTZ 6.25mg/day. Furthermore, there was a significantly greater reduction in BP with HCTZ 25mg/day compared with HCTZ 12.5mg/day, based on an indirect comparison. This observation was confirmed by performing a direct comparison between the doses from 7 of the studies. The pooled analysis showed that the combination of HCTZ 25mg/day plus ARB resulted in a significantly greater reduction in both SBP and DBP compared to the combination of HCTZ 12.5mg/day plus ARB [SBP -1.6 (95% CI -2.6, -0.5) mmHg; DBP -1.2 (95% CI -1.8, -0.5) mmHg].

A sensitivity analysis showed that the position of BP measurement did not significantly affect the results. Two of the trials [42,46] did not record the timing of BP.
measurement. Removal of these trials also did not change the results. Ten of the studies were industry sponsored and the source of funding was not reported for the other 3 studies so a sensitivity analysis could not be conducted.

3.4.1.3 Thiazide plus renin inhibitor vs renin inhibitor alone

Only one included study [59] was identified assessing the BP lowering efficacy of HCTZ plus renin inhibitor and the renin inhibitor alone. Three different doses of HCTZ were assessed (6.25mg/day, 12.5mg/day, and 25mg/day). Addition of HCTZ at each dose resulted in a significantly greater reduction in both SBP and DBP (Table 3.6). However, due to the lack of studies, there is insufficient data to conclude if there was a dose-response relationship.

Table 3.6: Additional BP reduction by adding a thiazide to a renin inhibitor. Fixed effect model (95%CI).

<table>
<thead>
<tr>
<th>Dose of Thiazide in multiples of starting dose</th>
<th># of studies</th>
<th>Total # of patients in combination group</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5x</td>
<td>1</td>
<td>360</td>
<td>-4.0 (-5.9, -2.2)</td>
<td>-1.8 (-3.0, -0.6)</td>
</tr>
<tr>
<td>1x</td>
<td>1</td>
<td>553</td>
<td>-5.2 (-6.8, -3.7)</td>
<td>-3.0 (-4.0, -2.1)</td>
</tr>
<tr>
<td>2x</td>
<td>1</td>
<td>546</td>
<td>-6.9 (-8.4, -5.4)</td>
<td>-3.5 (-4.5, -2.6)</td>
</tr>
</tbody>
</table>

3.4.1.4 Thiazide plus BB vs BB alone

Nine included studies assessing the BP lowering efficacy of thiazide plus beta-blocker and beta-blocker alone were identified. HCTZ 6.25 to 50mg/day was assessed in 7 studies, chlorthalidone 20mg/day in 1 study [6] and clopamide 10mg/day another study [51].
Based on the best available evidence, adding a thiazide at doses as low as 0.5x to 1x the manufacturer's recommended starting dose to a beta-blocker significantly reduced both SBP and DBP (see Table 3.7). Addition of thiazide 1.6x did not show a statistically significant additional BP reduction. However, this observation was based on only one small trial evaluating the BP lowering efficacy of chlorthalidone 20mg/day added to a beta-blocker, which included only 24 patients in the combination group for the efficacy analysis [6].

There was a trend towards greater BP reduction with higher doses of thiazides added. There were 5 studies evaluating the addition of a thiazide at 2x the starting dose. Pooling the data from these 5 studies showed an additional reduction of -8.2 (95% CI -10.3, -6.2) mmHg in SBP and -4.0 (95% CI -5.3, -2.8) mmHg in DBP. Three of the trials were measured at trough and the other two trials did not report when BP was measured. Removing these 2 studies did not significantly alter the overall BP effect size. The drugs were given once daily except in one trial [4] which HCTZ 12.5mg was given twice daily (BID). Four of the 5 studies evaluated HCTZ whereas the other study [51] evaluated clopamide 5mg given twice daily. A sensitivity analysis removing either of these studies did not change the overall additional BP effect size of thiazides added as a second drug to a beta-blocker.
A direct comparison of the BP lowering efficacy of adding HCTZ 12.5mg/day and 25mg/day to a beta-blocker could be performed in 2 of the included studies [25,40]. These studies were pooled and data showed that adding HCTZ 25mg/day resulted in a numerically greater systolic BP reduction than adding HCTZ 12.5mg/day, but this did not reach statistical significance.

The additional BP reduction resulting from the addition of thiazide 4x to a BB was assessed in 2 included studies (Table 3.7). The studies were fairly small in size with a total number of 31 patients in the combination group. As reflected by the wide confidence intervals, the estimate of the BP lowering efficacy at this dosage is imprecise.

3.4.1.5 Thiazide plus CCB vs CCB alone

There were 5 included studies assessing the BP lowering efficacy of thiazide plus CCB and CCB alone. Two of the studies assessed HCTZ given once daily [31, 60], another two studies assessed HCTZ given twice daily [44, 62], and one study assessed indapamide given once daily [48]. Due to the lack of studies for each of the different regimens, it was not possible to sufficiently analyze the effect of each regimen on BP (see Table 3.8).

Table 3.8: Additional BP reduction by adding a thiazide to CCB. Fixed effect model (95% CI).

<table>
<thead>
<tr>
<th>Dose of Thiazides in multiples of starting dose</th>
<th># of studies (SBP/DBP)</th>
<th>Total # of patients in combination group</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x</td>
<td>3</td>
<td>129</td>
<td>-3.7 (-6.7, -0.6)</td>
<td>-4.5 (-6.0, -2.9)</td>
</tr>
<tr>
<td>2x</td>
<td>2</td>
<td>137</td>
<td>-9.5 (-12.3, -6.6)</td>
<td>-5.9 (-7.6, -4.1)</td>
</tr>
</tbody>
</table>

Based on an indirect comparison, the addition of a thiazide at 2x the manufacturer’s starting dose to CCB resulted in a significantly greater reduction in BP compared with adding a thiazide at 1x the starting dose.
3.4.1.6 Thiazide plus centrally acting drug vs centrally acting drug alone

There is only one included study assessing the BP lowering efficacy of a thiazide plus a centrally acting drug versus a centrally acting drug alone. This was a fairly small trial with only 42 patients in the HCTZ 25mg/day plus moxonidine combination group and 37 patients in the moxonidine monotherapy group [16]. This trial showed that adding HCTZ 25mg/day resulted in an additional SBP reduction of -7.0 (95% CI -12.9, -1.1) mmHg and a DBP reduction of -4.0 (95% CI -7.8, -0.3) mmHg. However, as reflected by the wide confidence intervals, the precision of our estimate of the additional BP lowering efficacy of adding a thiazide to a centrally-acting drug is low.

3.4.1.7 Summary of the additional BP reduction induced by adding a thiazide to drug classes

Table 3.9 provides an overview of the additional BP reduction that was observed when a thiazide was given in combination with another class of antihypertensive drug. A graphical representation of the data can be seen in Figure 3.2. The dose of thiazides reviewed ranged from 0.4x to 4x the manufacturer’s recommended starting dose. It is evident that the addition of a thiazide within this dose-range as the second-drug resulted in a statistically significant additional BP reduction. The magnitude of the additional SBP/DBP reduction ranged from 4/2 to 14/6 mmHg.

Table 3.9: Summary of the additional BP reduction of thiazide as a second drug in combination therapy

<table>
<thead>
<tr>
<th>Dose of Thiazides (multiples of starting dose)</th>
<th># of studies (SBP/DBP)</th>
<th>Total # of patients in combination group (SBP/DBP)</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5x</td>
<td>10/12</td>
<td>1563/1677</td>
<td>-3.7 (-4.6, -2.8)</td>
<td>-1.7 (-2.2, -1.2)</td>
</tr>
<tr>
<td>1x</td>
<td>33/36</td>
<td>4190/4352</td>
<td>-6.0 (-6.5, -5.4)</td>
<td>-3.1 (-3.4, -2.8)</td>
</tr>
<tr>
<td>2x</td>
<td>25/29</td>
<td>3022/3269</td>
<td>-8.0 (-8.7, -7.3)</td>
<td>-4.1 (-4.5, -3.7)</td>
</tr>
<tr>
<td>3x-4x</td>
<td>4/4</td>
<td>185/185</td>
<td>-14.2 (-17.2, -11.3)</td>
<td>-6.0 (-7.7, -4.3)</td>
</tr>
</tbody>
</table>
A dose-response relationship can be established in which higher doses of thiazides resulted in a statistically significant greater reduction in BP. However, data were limited for thiazides greater than 2x the starting dose. There is one study assessing thiazide 3x (OD dosing), one study assessing thiazide 3.6x (TID dosing), and 2 studies assessing thiazide 4x (TID dosing). Pooled analysis of these 4 studies showed that the additional reduction in SBP and DBP with thiazides 3x-4x was -14.2 (95% CI -17.2, -11.3) mmHg and -6.0 (95% CI -7.7, -4.3) mmHg, respectively. Although indirect comparisons showed that thiazide 3x-4x resulted an additional BP reduction that was statistically higher than those achieved with thiazides 2x, no solid conclusions could be made about the difference because of the lack of studies and the difference in dosing schedules. Moreover, both of the studies assessing thiazides 4x were judged to have a high risk of incomplete outcome data bias (38, 58).

### 3.4.1.8 Subgroup analysis

A majority of the data were for HCTZ 12.5mg/day and HCTZ 25mg/day. A subgroup analysis was done to determine whether the first drug has a significant effect on the
BP lowering of thiazide given as a second drug.

As shown in Figure 3.3, the additional BP reductions induced by adding HCTZ 12.5mg/day to another class of anti-hypertensive drugs were similar with overlapping 95% confidence intervals. However, based on indirect comparisons, the additional systolic BP reduction with HCTZ 12.5mg/day was significantly greater when added to an ARB as compared to an ACEI or a renin inhibitor. Since these 3 classes of drugs are believed to lower BP by inhibiting the renin-angiotensin-aldosterone system (RAAS), albeit at different levels, one would not expect that adding HCTZ to one class would be different from adding it to the other in terms of magnitude of BP reduction. Furthermore, when HCTZ 25mg/day was added to the other antihypertensive drugs, the class of drugs to which HCTZ was added to did not have a statistically significant effect on the magnitude of the additional BP reduction (Figure 3.4). Therefore, the difference that was found between adding HCTZ 12.5mg/day to ARB and to the other drug classes is likely to be due to chance.

Figure 3.3. Additional BP change (± 95% CI) induced by HCTZ 12.5mg/day in combination therapy with the following drugs.
3.4.1.9 Comparison of BP reduction achieved by HCTZ in combination therapy and in monotherapy

The BP lowering efficacy of HCTZ monotherapy versus placebo in patients with mild to moderate primary hypertension has been determined in a systematic review by Musini 2000 [120]. By performing an indirect comparison of the results between this current review and that of Musini 2000, we can investigate whether the additional BP achieved by adding HCTZ as the second drug in combination therapy differs from that achieved by administering HCTZ alone as monotherapy.

Based on the best available evidence, the estimated additional BP that can be expected when HCTZ 12.5mg/day is added as a second drug is -6.0 (95% CI -6.5, -5.4) mmHg for SBP and -3.1 (95% CI -3.4, -2.8) mmHg for DBP. The estimated additional BP reduction that can be expected with the addition of HCTZ 25mg/day as a second-line drug is -8.0 (95% CI -8.7, -7.3) mmHg for SBP and -4.0 (95% CI -4.4, -3.6) mmHg for DBP. The results from Musini 2000 showed that BP lowering efficacy of HCTZ as a first-line agent versus placebo is a reduction of -5.7 (-7.0, -4.5) mmHg in SBP and -3.9 (-
4.7, -3.0) mmHg in DBP for HCTZ 12.5mg/day and -8.5 (-10.4, -6.6) mmHg in SBP and -4.7 (-5.8, -3.5) mmHg in DBP for 25mg/day (see Table 3.10 and Table 3.11).

Table 3.10 : SBP reduction contributed to HCTZ added in combination with other drugs or as a single drug. Fixed effect model (95%CI).

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>SBP reduction (mmHg)</th>
<th># patients in combination group</th>
<th>HCTZ as monotherapy*</th>
<th># patients in HCTZ group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5 mg/day</td>
<td>-6.0 (-6.5, -5.4)</td>
<td>4190</td>
<td>-5.7 (-7.0, -4.5)</td>
<td>579</td>
<td>NS</td>
</tr>
<tr>
<td>HCTZ 25 mg/day</td>
<td>-8.0 (-8.7, -7.3)</td>
<td>2913</td>
<td>-8.5 (-10.4, -6.6)</td>
<td>368</td>
<td>NS</td>
</tr>
</tbody>
</table>

*adopted from Musini 2000 [120]

Indirect comparison showed that the additional SBP reduction that resulted from the addition of HCTZ 12.5mg/day or HCTZ 25mg/day to another class of drugs was not statistically different from the SBP reduction induced by HCTZ 12.5mg/day or HCTZ 25mg/day monotherapy, respectively (Table 3.10).

Table 3.11 : DBP reduction contributed to HCTZ added in combination with other drugs or as a single drug. Fixed effect model (95%CI).

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>DBP reduction (mmHg)</th>
<th># patients in combination group</th>
<th>HCTZ as monotherapy*</th>
<th># patients in HCTZ group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5 mg/day</td>
<td>-3.1 (-3.4, -2.8)</td>
<td>4279</td>
<td>-3.9 (-4.7, -3.0)</td>
<td>579</td>
<td>NS</td>
</tr>
<tr>
<td>HCTZ 25 mg/day</td>
<td>-4.0 (-4.4, -3.6)</td>
<td>3093</td>
<td>-4.7 (-5.8, -3.5)</td>
<td>368</td>
<td>NS</td>
</tr>
</tbody>
</table>

*adopted from Musini 2000 [120]

The same conclusion was made for DBP reductions (Table 3.11). The additional SBP reduction that resulted from the addition of HCTZ 12.5mg/day or HCTZ 25mg/day to another class of drugs was not statistically different from the DBP reduction induced by HCTZ 12.5mg/day or HCTZ 25mg/day monotherapy, respectively.

3.4.2 Loop diuretic plus other drug vs other drug alone

By comparing the difference in BP reduction between combination therapy (a loop diuretic + 1 other drug) and monotherapy (placebo or no treatment + 1 other drug)
groups, the additional BP reduction resulting from adding a loop diuretic as the second drug was estimated.

### 3.4.2.1 Loop diuretic plus ACEI vs ACEI alone

There are two included studies assessing the BP lowering efficacy of the combination of piretanide and ACEI versus ACEI alone [21, 57]. The first study (Homuth 1993) [21] assessed two different doses of piretanide (3mg/day and 6mg/day) whereas the other study [57] included only one dose (6mg/day). No included studies assessed piretanide at any other doses in combination with an ACEI. Homuth 1993 showed that the addition of piretanide 3mg/day, which corresponds to 0.5x the manufacturer's recommended starting dose, to ACEI did not result in a significant additional BP reduction. At 1x the starting dose, a statistically significant additional BP reduction was observed when the results from both studies were pooled (see Table 3.12)

#### Table 3.12: Additional BP reduction by adding a loop diuretic to ACEI. Fixed effect model (95%CI).

<table>
<thead>
<tr>
<th>Dose of loop diuretic (multiples of starting dose)</th>
<th># of studies</th>
<th>Total # of patients in combination group</th>
<th>Change in SBP (95% CI) mmHg</th>
<th>Change in DBP (95% CI) mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5x</td>
<td>1</td>
<td>120</td>
<td>-1.8 (-5.2, +1.6)</td>
<td>-0.4 (-2.5, +1.7)</td>
</tr>
<tr>
<td>1x</td>
<td>2</td>
<td>312</td>
<td>-6.5 (-8.7, -4.2)</td>
<td>-3.1 (-4.5, -1.7)</td>
</tr>
</tbody>
</table>

### 3.4.2.2 Loop diuretic plus BB vs BB alone

Only one included study [10] compared the BP lowering efficacy of a loop diuretic plus a beta-blocker versus a beta-blocker alone. In this study, the combination group was given frusemide 20mg/day plus a beta blocker. There were only 16 patients in the combination group and 11 patients in the beta-blocker monotherapy group. Therefore, due to the lack of data for this combination, our effect estimates have extremely wide
confidence intervals, and is therefore imprecise [-13.0 (95% CI -33.0, -7.0) mmHg SBP; -8.0 (95% CI -19.0, +3.0) mmHg DBP].

3.5 Pulse pressure

Pulse Pressure (PP) was not reported as an outcome in any of the included studies. Therefore, the value of change in PP was calculated by subtracting DBP change from SBP change for each treatment arm in the trial. Using this approach, the change in PP can only be calculated from trials that provided data for both SBP and DBP.

3.5.1 Thiazides

Both SBP and DBP data was provided in 47/49 (96%) included studies assessing HCTZ. The data demonstrated a trend towards higher PP reduction with increasing doses of HCTZ in the combination group (Table 3.13).

Table 3.13: Pulse pressure reduction at end of treatment. Combination therapy versus monotherapy: Hydrochlorothiazide as a second drug.

<table>
<thead>
<tr>
<th>Hydrochlorothiazide (multiples of starting dose)</th>
<th># of studies</th>
<th># of patients (combo/mono)</th>
<th>Weighted mean change in pulse pressure (95% CI) – combination group (with HCTZ)</th>
<th>Weighted mean change in pulse pressure (95% CI) - monotherapy group (no HCTZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5x</td>
<td>10</td>
<td>1563/1720</td>
<td>-3.1 (-4.4, -1.9)</td>
<td>-1.3 (-2.3, -0.3)</td>
</tr>
<tr>
<td>1x</td>
<td>30</td>
<td>3974/4072</td>
<td>-5.9 (-7.6, -3.8)</td>
<td>-3.0 (-4.4, -1.6)</td>
</tr>
<tr>
<td>2x</td>
<td>22</td>
<td>2913/2886</td>
<td>-8.6 (-11.4, -5.9)</td>
<td>-4.0 (-6.2, -1.8)</td>
</tr>
<tr>
<td>3x-4x</td>
<td>4</td>
<td>185/182</td>
<td>-6.8 (-12.2, -1.4)</td>
<td>+0.7 (-0.7, +2.2)</td>
</tr>
</tbody>
</table>

An estimate of the reduction in PP achieved by indapamide, clopamide or chlorthalidone (as a second drug) cannot be estimated separately because data was obtained from 1 study each. Pooling of data from all thiazides did not significantly alter the results. However, pooling of data for all thiazides did not significantly alter the results. To determine the additional effect of all thiazides as a second drug on PP, the data for indapamide, clopamide and chlorthalidone were combined with HCTZ (Table 3.14).
There was a trend towards a greater PP reduction with higher doses of thiazides with an additional reduction in PP of -7.5 (95% CI -11.9, -3.2) mmHg with thiazide 3-4x.

**Table 3.14 : Difference in pulse pressure reduction at end of treatment. Combination therapy versus monotherapy: Thiazides as a second drug class.**

<table>
<thead>
<tr>
<th>Thiazides (multiples of starting dose)</th>
<th># studies</th>
<th>Difference in PP between combination and monotherapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5x</td>
<td>10</td>
<td>-1.7 (-3.2, -0.1)</td>
</tr>
<tr>
<td>1x</td>
<td>30</td>
<td>-2.8 (-5.0, -0.7)</td>
</tr>
<tr>
<td>2x</td>
<td>25</td>
<td>-4.7 (-6.9, -2.4)</td>
</tr>
<tr>
<td>3x-4x</td>
<td>4</td>
<td>-7.5 (-11.9, -3.2)</td>
</tr>
</tbody>
</table>

### 3.5.2 Loop diuretics

Due to the lack of studies with the loop diuretics, the reduction in pulse pressure (PP) cannot be estimated.

### 3.6 Blood pressure variability

#### 3.6.1 Thiazides

**3.6.1.1 Baseline variability**

The standard deviation (variability) of BP at baseline was reported in 27/53 (51%) included studies. There was no statistically significant difference between the variability of SBP (p=0.6) or of DBP (P=0.5) at baseline between the combination and monotherapy groups (Table 3.15).

**Table 3.15 : Variability of SBP and DBP at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Combo group</th>
<th>Mono group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>14.1</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>1.8</td>
</tr>
<tr>
<td>DBP</td>
<td>4.7</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

#### 3.6.1.2 Baseline vs endpoint variability

The standard deviations of BP at baseline (after the run-in period) and the standard deviations of BP at endpoint were compared in 9 included studies. As shown in Table 3.16, there was no statistically significant difference between the SBP variability at
baseline and endpoint in the combination group or in the monotherapy group. For DBP variability, the baseline SDs were statistically significantly lower than the endpoint values in both the combination and monotherapy groups, an effect likely due to the fact that all studies had DBP entry criteria [121].

**Table 3.16 : Standard deviations of BP at baseline vs. endpoint in trials with DBP entry criteria**

<table>
<thead>
<tr>
<th></th>
<th>Combination group</th>
<th>Monotherapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weighted mean SD of SBP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline (SD)</td>
<td>14.1 (2.2)</td>
<td>14.3 (2.5)</td>
</tr>
<tr>
<td>At endpoint (SD)</td>
<td>15.7 (1.9)</td>
<td>16.0 (2.2)</td>
</tr>
<tr>
<td>t-test baseline vs. Endpoint</td>
<td>p = 0.1</td>
<td>p = 0.3</td>
</tr>
<tr>
<td><strong>Weighted mean SD of DBP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline (SD)</td>
<td>5.0 (0.9)</td>
<td>4.9 (0.9)</td>
</tr>
<tr>
<td>At endpoint (SD)</td>
<td>8.6 (1.1)</td>
<td>8.4 (1.0)</td>
</tr>
<tr>
<td>t-test baseline vs. endpoint</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

3.6.1.3 **Combination vs monotherapy**

To determine if the addition of thiazides affects the BP variability, the standard deviations of BP at the end of treatment were compared between the combination therapy and monotherapy groups. The standard deviation (variability) of BP at endpoint was reported in 9 included studies. As shown in Table 3.16, the weighted mean SD of SBP at the end of treatment was 15.7 mm Hg for the combination group, and 16.0 mm Hg for the monotherapy group. The weighted mean SD of DBP at the end of treatment was 8.6 mm Hg for the combination group, and 8.4 mm Hg for the monotherapy group. Variability of BP was not significantly different between the combination group and monotherapy group for both SBP (p=0.8) and DBP (p=0.7).

3.6.2 **Loop diuretics**

Due to the lack of studies with the loop diuretics, their effects on BP variability could not be estimated.
3.7 Heart rate

3.7.1 Thiazides

Heart data are shown in Table 3.17. Heart rate data were extracted from 6 (11%) included studies of which 4 studies involved the combination with a HCTZ [4,18,31,58]. The addition of HCTZ to another antihypertensive drug class did not show a statistically significant change in heart rate [+0.5 (95%CI -1.1, 2.1) beats/min]. There was one trial each for clopamide [51] and chlorthalidone [6] so no conclusions could be drawn about their effect on heart rate.

Table 3.17: The additional heart rate effects of adding a thiazide as the second drug. Fixed effect model (95%CI)

<table>
<thead>
<tr>
<th>Thiazides</th>
<th># of trials</th>
<th>Total # of patients in combination group</th>
<th>Change in HR, beats/minute (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ</td>
<td>5</td>
<td>229</td>
<td>+0.5 (-1.1, +2.1)</td>
</tr>
<tr>
<td>Clopamide</td>
<td>1</td>
<td>15</td>
<td>+7.8 (-2.7, +18.3)</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>1</td>
<td>24</td>
<td>-3.0 (-9.7, +3.7)</td>
</tr>
</tbody>
</table>

3.7.2 Loop diuretics

None of the included studies assessing loop diuretics provided heart rate data.

3.8 Withdrawals due to adverse effects

3.8.1 Thiazides

Data on WDAEs during the 3 to 12 weeks of treatment were extracted from 35/53 (66%) of the included studies for analysis.

Table 3.18: Withdrawals due to adverse effects: drug/thiazide vs drug alone

<table>
<thead>
<tr>
<th>Drug comparisons</th>
<th># of trials</th>
<th># of WDAE in combination vs monotherapy groups</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/Thiazide vs ACEI</td>
<td>13</td>
<td>53/1508 vs 36/1097</td>
<td>0.94 (0.62, 1.44)</td>
</tr>
<tr>
<td>ARB/Thiazide vs ARB</td>
<td>9</td>
<td>82/2456 vs 33/1222</td>
<td>1.14 (0.62, 1.71)</td>
</tr>
<tr>
<td>BB/Thiazide vs BB</td>
<td>5</td>
<td>4/215 vs 3/153</td>
<td>1.02 (0.33, 3.16)</td>
</tr>
<tr>
<td>CCB/Thiazide vs CCB</td>
<td>2</td>
<td>2/97 vs 1/94</td>
<td>1.63 (0.22, 11.98)</td>
</tr>
<tr>
<td>CAD/Thiazide vs CAD</td>
<td>1</td>
<td>1/42 vs 2/37</td>
<td>0.44 (0.04, 4.91)</td>
</tr>
<tr>
<td>Renin/thiazide vs Renin</td>
<td>1</td>
<td>36/1459 vs 9/546</td>
<td>1.5 (0.73, 3.09)</td>
</tr>
</tbody>
</table>
Of the 35 trials that reported WDAE, 4 studies reported no WDAE in both combination and monotherapy groups. Overall, 178/5944 (3%) of the patients in the combination group withdrew due to adverse effects compared with 84/3314 (2.5%) of the patients in the monotherapy group. There was no statistically significant difference in WDAE between the combination and monotherapy groups [RR 1.09 (95% CI 0.84, 1.42)].

3.8.2 Loop diuretics

Based on 2 included studies, adding a loop diuretic as the second drug was not shown to have any significant impact on the number of withdrawals due to adverse effects (see Table 3.19).

Table 3.19: Withdrawals due to adverse effects: drug/loop diuretic vs drug alone

<table>
<thead>
<tr>
<th>Drug comparisons</th>
<th># of trials</th>
<th># of WDAE in combination vs monotherapy groups</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB/Loop diuretic vs BB</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>ACEI/Loop diuretic vs ACEI</td>
<td>2</td>
<td>6/441 vs 3/329</td>
<td>0.94 (0.25, 3.5)</td>
</tr>
</tbody>
</table>
3.9 References


8. Camera MI, Waisman GD, Galarza CR, Alfie J, Arahabety A, Saggese O, Magi MI, Mayorga LM. Multi-centre study of the antihypertensive effect of lisinopril (20 mg) and a fixed combination of lisinopril (20 mg) and hydrochlorothiazide (12.5 mg) once daily in mild to moderate essential hypertension.. Drug Development Research. 1995;34(suppl. 2):20-23. [Other: EMBASE 1995095667; CN-00169283]


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65. Agrawal RL. Double-blind comparison of Inderal LA (160mg), Half-Inderal LA (80 mg), and Half-Inderal LA plus bendrofluazide (2.5mg) in the treatment of elderly hypertensive patients. The British Journal of Clinical Practice 1987;41:916-920.


70. Bolzano K, Kremler F, Sandhofer F. [A combination of methyldopa, hydrochlorothiazide and amiloride in the treatment of essential hypertension] [Eine


95. Magee PFA, Freis ED. Is Low-Dose Hydrochlorothiazide Effective? Hypertension 1986;8 (suppl II).


4 DISCUSSION

Diuretics are widely prescribed for the treatment of hypertension. In the majority of patients without a compelling indication for another class of drug, a low dose of diuretic should be considered as the first drug of choice in patients with mild to moderate hypertension [1]. It has been demonstrated that a low dose of thiazide, generally started with the equivalent of 12.5 mg to 25 mg per day of chlorthalidone or hydrochlorothiazide, reduces the risk of total mortality, strokes, and coronary artery disease compared to placebo or no treatment [2, 3].

In this review, giving a diuretic as second-line therapy in combination therapy to patients with primary essential hypertension has been shown to further reduce BP in a dose-related manner without increasing withdrawals due to adverse effects.

4.1 What are some issues encountered in the search strategy?

The standard search strategy of the Cochrane Hypertension review group was employed. However, it was not possible to modify the search strategy to identify only trials that involved both combination and monotherapy groups. The term “combination” cannot be used in the search to limit trials to those that involved at least a combination group because not all trials that used combination therapy were tagged with the keyword “combination”. To maintain high sensitivity and specificity, we included trials that had assessed at least 2 different drug classes. The result is that many irrelevant trials had to be excluded after reading the abstract. Of the studies that were methodologically acceptable, many did not provide the data required for meta-analysis. A number of studies initially thought to be eligible were excluded as the data needed was not available.
in the publication. The majority excluded were crossover studies which did not report data from the first treatment period separately.

4.2 **What is the additional BP reduction of thiazide and thiazide-like diuretics when added to other classes of antihypertensive drugs?**

Blood pressure efficacy data for the thiazide class was extracted from 53 included studies. Since most of the studies included multiple comparison treatment arms, not all data were extracted for this review. Only data that addressed the comparisons relevant to this review were included. These data were taken from a total of 15129 hypertensive patients, 9483 treated with combination therapy and 5646 treated with monotherapy. These patients had a BP at baseline averaging 156/101 mmHg and a mean age of 54 years. These studies ranged from 3 to 12 weeks with an average 6-week double-blind treatment period.

By comparing the difference in BP reduction between the combination (thiazide + 1 other drug) and monotherapy (placebo or no treatment + 1 other drug) groups, the additional BP reduction with a thiazide as second-line therapy was estimated. Hydrochlorothiazide was assessed in 49/53 (92%) of the included studies.

The contribution of the thiazide component was statistically significant in terms of the magnitude of BP reduction. Participants who received combination therapy (with a thiazide) experienced greater reductions in both systolic and diastolic BP than participants receiving monotherapy (without thiazide). This is evident at all doses that were assessed in the review. The decrease in SBP/DBP ranged from an additional 4/2 mmHg for lower dose thiazides to 14/6 mmHg for higher dose thiazides.
In this review, the doses of thiazides have been categorized according to multiples of the manufacturer’s recommended starting dose ranging from 0.4x to 4x and data were pooled based on this categorization. A dose-response relationship was demonstrated at each increment of thiazide dose. This represents a very robust demonstration that the BP lowering effect of thiazides is dose-dependent.

It is worth noting that the data are based primarily on white patients. Although non-white (blacks and others) patients were included in the efficacy analysis, they consisted of only a minority of the patients and most studies did not provide separate data for this subgroup. Therefore, our results are mostly generalizable to white hypertensive patients.

4.3 What is the additional BP reduction of loop diuretics when given in addition to another class of antihypertensive drugs?

There are limited data available for the BP lowering efficacy of loop diuretic as a second drug. Only three included studies provided these data. Adding a loop diuretic as a second drug was effective starting at 1x the manufacturer’s recommended dose, resulting in an additional reduction of -6.5 (95% CI -9.0, -4.0) mmHg in SBP and -3.1 (95% CI -4.5, -1.7) mmHg in DBP. There were no included studies assessing second-line loop diuretic at doses greater than 1x the manufacturer’s starting dose.

4.4 Is there a difference in the reduction of blood pressure between adding a thiazide to different classes of drugs?

As described above, the available data have demonstrated a dose-related BP lowering effect of thiazides as a second-line drug over the range of 0.4x to 4x the manufacturer’s recommended starting dose. In order to determine if there were a
difference in the additional BP reduction achieved between adding thiazides to different classes of first-line drugs, comparisons were made for the doses of HCTZ that had the most available data, 12.5mg/day and 25mg/day. Based on indirect comparisons, the choice of the first drug did not have a significant effect on the additional BP lowering of a thiazide when given as a second-line drug. A more direct way of assessing if the addition of a thiazide to different drug classes leads to differences in BP lowering would be by meta-analyzing head-to-head combination trials where the same dose of HCTZ was added to two different classes of drugs. The data here give a pretty good indication that the effect is independent of the first-line drug, a finding that was not expected. Based on their proposed mechanisms of action, most clinicians believe that adding a thiazide to an ACE inhibitor or ARB would have a greater effect than adding a thiazide to a CCB.

4.5 Is there a difference in the blood pressure lowering efficacy of diuretics given as initial therapy or as a second line drug in combination therapy?

In order to determine whether there is a difference in the BP lowering efficacy of HCTZ given as monotherapy or as a second drug in combination therapy, the magnitude of BP reduction was compared. The BP lowering efficacy of diuretics monotherapy (as a first-line drug) versus placebo in patients with mild to moderate primary hypertension was previously assessed in a systematic review by Musini 2000 [4]. Based on the available data, HCTZ demonstrated a dose-related reduction in BP compared to placebo. Results from that review showed that HCTZ 12.5mg/day and 25mg/day decreased SBP by -5.7 (95% CI -7.0, -4.5) mmHg and -8.5 (95% CI -10.4, -6.6) mmHg, respectively. The reduction in DBP were -3.9 (95% CI -4.7, -3.0) mmHg and -4.7 (95% CI -5.8, -3.5) mmHg, respectively. In our review, the BP lowering efficacy of HCTZ as a second drug
in the treatment of hypertension was estimated to be -6.0 (95% CI -6.5, -5.4) mmHg for SBP and -3.1 (95% CI -3.4, -2.8) mmHg for DBP at 12.5mg/day, and -8.0 (95% CI -8.7, -7.3) mmHg for SBP and -4.0 (95% CI -4.4, -3.6) mmHg for DBP at 25mg/day. As summarized in Table 3.10 and Table 3.11, the magnitude of BP lowering with HCTZ as a first-line drug and as a second-line drug is remarkably similar and not statistically significantly different. Therefore, our review has demonstrated that HCTZ has a similar BP lowering efficacy as first-line and second-line therapy, and that the BP lowering effect of HCTZ as second-line therapy is additive.

**4.6 Does age have an effect on BP lowering of diuretics?**

The age inclusion criteria for most studies ranged from 18 to 80 with an average of 54 years. There was only one study that included only elderly patients [5] with a mean age of 71 yrs. Due to the lack of reporting and limited data, a subgroup analysis of older versus younger patients could not be performed.

**4.7 Does co-morbidity have an effect on BP lowering of diuretics?**

It was not possible to perform a subgroup analysis of hypertensive patients with other co-morbid diseases. None of the trials specifically selected for patients with co-morbid conditions and the majority of the studies excluded patients with significant major diseases including renal, cardiovascular, hepatic and neurologic problems. Furthermore, data for these subgroups of patients, if included, have not been reported separately.

**4.8 What is the effect of second-line diuretics on BP variability?**

The standard deviations (SD) of the BP at baseline and/or endpoint were reported in 27/53 (51%) of the included studies. The endpoint variabilities of the combination and monotherapy groups were compared in order to determine the effect of adding diuretics
as a second drug on BP variability. The values used to determine endpoint variability were based on endpoint SDs. Analysis of the available data showed that adding diuretic as second-line therapy did not alter variability of resting SBP and DBP variability since there were no statistically differences between the combination and the monotherapy groups. Because mean values are used, both inter- and intra-individual variabilities were accounted for. To determine the effects on intra-individual variability, 24-hr blood pressure monitoring would be needed.

BP criteria for entry into the trial was likely to affect the variability at baseline. The baseline variability in DBP has been shown in other reviews to be statistically lower than the endpoint values in trials with DBP entry criteria for both treated (monotherapy) and untreated (placebo) groups [6-9]. Consistent with these findings, the same trend was observed in this review. For both combination and monotherapy groups, baseline SD values for DBP were similar between both groups but were both significantly lower than endpoint values (p<0.0001). This effect is likely due to the inclusion of many patients near the DBP threshold level for entry into the trial and to the truncation of the distribution of blood pressures at this threshold. None of the trials which provided standard deviations had only SBP entry criteria and therefore it was not possible to determine the effect of SBP entry criteria on SBP variability at baseline.

4.9 What is the effect of second-line diuretics on pulse pressure?

Pulse pressure (PP) has become increasingly recognized as an independent risk factor for cardiovascular events [10,11]. Although PP has not been indicated as one of the primary or secondary endpoints in any of the included studies, we were able to calculate it from trials that provided both SBP and DBP data. Fifty-one (96%) of the studies
assessing a thiazide provided both SBP and DBP data whereas the other 2 studies only reported DBP data. By subtracting the change in DBP from the change in SBP for each of the 51 trials, it was found that PP was significantly reduced by adding a thiazide as a second drug at the dose range studied (0.4x to 4x the manufacturer’s recommended starting dose). There is a possibility of a dose-response relationship because there was a trend towards a greater reduction of PP with higher doses of thiazides (see Table 3.14). PP was further reduced by -1.7 (95% CI -3.2, -0.1) mmHg with the addition of thiazide ≤0.5x to as much as -7.5 (95% CI -11.9, -3.2) mmHg with thiazide 3x-4x. Hydrochlorothiazide was the thiazide used in all except 3 studies [12,13,14]. Removal of these 3 studies in sensitivity analysis did not significantly alter the results.

Because there were only 3 studies assessing loop diuretics at various doses, their effects on pulse pressure could not be assessed in this review.

4.10 What is the effect of second-line diuretics on heart rate?

The results for heart rate outcome were reported incompletely in many of the studies, where only p-values were given or changes were described as “not significantly different”. For the loop diuretics, there were no included studies providing heart rate data for analysis. Quantitative heart rate data could only be extracted from 6 (11%) of the included studies assessing thiazides. Pooled analysis of these 6 trials showed that addition of a thiazide to another antihypertensive drug did not significantly affect heart rate [+0.4 (95% CI -1.1, +2.0) beats/min].
4.11 What is the effect of second-line diuretics on withdrawals due to adverse effects?

For the thiazides, the number of withdrawals due to adverse effects within 3-12 week treatment period was reported in 35/53 (66%) of the included studies. Consistent with the data for thiazides given as monotherapy [4], adding a thiazide as a second-line drug did not result in a significant increase or reduction in withdrawals due to adverse effects [RR 1.09 (95% CI 0.84, 1.42)]. The type of drug class to which thiazides was added also did not seem to significantly affect the results. Not all studies reported the reason for withdrawals, and the total adverse events in the studies were, on average, not statistically different between combination and monotherapy groups. It is worth noting that most studies excluded patients with previous known allergic reactions to diuretics or any of the drugs used in the studies. Therefore, this review is not a good assessment of adverse effects in a general population taking the drugs for long-term therapy.

Because of the lack of identified trials, WDAE data for loop diuretics are very limited. Meta-analysis of 2 studies where a loop diuretic was added to ACEI shows that WDAE was not significantly changed [RR 0.94 (95CI 0.25, 3.5)] as compared to ACEI monotherapy.

4.12 What are the potential sources of bias in this systematic review?

The risk of bias in the included studies was assessed individually using the Cochrane Collaboration's recommended tool. The criteria for judging risk of bias can be found in section 8.5 of the Cochrane Handbook for Systematic Review of Intervention [15]. (See Appendix B for the review author’s judgments about each methodological quality item presented as percentages across all included studies)
4.12.1 Sequence generation and allocation concealment

There was an unclear risk of bias in all the included studies in terms of sequence generation and allocation concealment due to poor reporting. The authors merely stated “randomly assigned” or “using a randomized design” without defining the process or the approach used. Authors should report their methods of sequence generation and allocation concealment clearly.

4.12.2 Blinding

Only double-blind, randomized, controlled trials were considered eligible for this review. Nearly all the trials merely stated that the trial was “double-blind” without providing further details about the blinding methods employed. Moreover, none of the studies tested whether the double-blind procedure was successful at the end of the study. Blinding of the patient to either diuretic treatment or non-diuretic treatment could have been broken as patients on diuretics might have noticed increased urine output in the first few days of active treatment.

4.12.3 Incomplete outcome data

There was inconsistency in the methods of analysis and reporting of results. In a majority of the trials, not all patients randomized were included in the BP efficacy analysis as only those patients who did not violate the protocols or who completed the entire trial (i.e. per-protocol analysis and complete-patient analysis) were included. However, the number of randomized patients included in the efficacy analysis was greater than 80% in all except 6 studies [5, 13, 16, 17, 18, 19]. In Hart 1991 [5], 153/299 (51%) of the patients were included in the per-protocol analysis. In the other 5 studies, about 25-38% of the randomized patients were missing in the treatment arms in the
efficacy analysis. In this review, exclusion of more than 20% of the randomized patients was judged to have a high risk of bias. The majority of the other included studies were judged to have a low risk of bias in terms of incomplete outcome data.

4.12.4 Selective outcome reporting

All the included studies provided data on the change in BP, which was the primary outcome of this review. However, there were 4 studies that provided DBP without SBP data. There is a possibility of selective reporting bias for heart rate and withdrawals due to adverse effects since only 11% and 66% of the trials reported these outcomes, respectively.

4.12.5 Other potential sources of bias

4.12.5.1 Publication Bias

Publication bias, defined in this review as the selective publication of studies with positive results, is another source of bias that may have skewed the results of this review. The most common way to investigate whether or not an effect estimate is subject to publication bias is to examine for funnel plot asymmetry. The funnel plots appeared reasonably symmetrical upon visual examination of the funnel plots. However, funnel plots cannot be investigated adequately in this review because each comparison in this review was set up according to treatment arms (i.e. the unit of analysis is treatment arm and not the entire study as a whole).

4.12.5.2 Selection Bias

The method of recruitment of the participants for the trials may serve as another source of bias. Studies may have selected participants who are previously known to be responders to diuretics, either as a first-line drug or second-line drug. This may result in
an overestimation of the effect size of the BP lowering efficacy of the diuretics, as compared to the typical BP response observed in the general population taking diuretics. However, the degree of selection bias could not be assessed because the types of patients recruited were not described adequately. Also, in most studies, participants who were known to have allergic reactions to diuretics or any of the drugs used in the particular trial were excluded. Thus, these trials would have underestimated the incidence of adverse effects or withdrawals due to adverse effects associated with diuretics.

4.12.5.3 Funding

28/56 (50%) of the included studies were industry sponsored. The other 28 (50%) studies did not report any funding source. Therefore, it was not possible to compare the results between industry funded and non-industry funded trials because there were no trials that were reported as being non-industry funded.

4.12.5.4 Other factors

Most BP measurements were taken just before the next dosing schedule (i.e. trough) in this review. However, 12/56 (21%) studies were included that did not mention the timing of the measurement. If these studies all measured peak BP, and diuretics have a greater BP lowering effect at peak as compared to trough, then including these 12 studies in the overall effect estimate may result in an overestimation of the trough BP lowering efficacy of diuretics. However, a sensitivity analysis excluding these 12 trials did not result in statistically significant difference in the effect estimate so including these trials and assuming they were taken at trough seems reasonable.
4.13 References


5 CLINICAL IMPLICATIONS

This systematic review provides the best available evidence of the additional BP lowering efficacy of diuretics as a second drug in combination therapy for the treatment of primary hypertension.

Findings of this review

1. Adding a thiazide diuretic as second-line agent in combination therapy resulted in a greater reduction in BP as compared to monotherapy (without thiazide).

2. The additional BP reduction induced by thiazides was dose-dependent. The SBP/DBP decreased further from baseline with the addition of a thiazide by 4/2, 6/3, 8/4, 14/6 mmHg at doses ≤0.5x, 1x, 2x and 3x-4x respectively.

3. There was a trend towards a dose related pulse pressure reduction with thiazides.

4. Adding a thiazide diuretic as second-line therapy does not affect resting BP variability.

5. Adding a thiazide diuretic as second-line therapy does not affect resting heart rate.

6. Adding a thiazide diuretic as second-line therapy did not change the rate of withdrawals due to adverse events within 3-12 weeks treatment period. However, only 35/53 (66%) of the studies reported this outcome and there is a possibility for selective outcome reporting bias.

7. The magnitude of the BP reduction achieved by HCTZ given as a second-line drug is similar to the magnitude of BP lowering for HCTZ alone. Thus the BP lowering effect is additive.

8. The drug class to which thiazide was added did not appear to affect the additional BP lowering of the thiazide.
9. The evidence for loop diuretics is weak but they appear to reduce BP by 6/3 mmHg at the recommended starting dose.

Implications of findings

Thiazides produce a reproducible dose related additive blood pressure lowering effect when given as the second drug for hypertension.
6 RESEARCH IMPLICATIONS

1. Since systematic reviews are secondary analyses of the data obtain from primary research, the validity of the results are dependent on the quality of the primary trials. The quality of reporting of the clinical trials should be improved to provide complete information on the following parameters:

   A) Methodological details: methods of randomization, blinding and allocation concealment.
   B) Complete baseline characteristic details of randomized patients: age, sex, race, baseline BP, other co-morbid illnesses, number of patients who were previously treated with the drug of interested and their response.
   C) Baseline BP and endpoint BP, the mean change from baseline for all treatment visits. The standard deviations of all of these parameters should also be reported. Values should be reported in tables and not in graphs/figures.
   D) The number of patients completing the trial and the number of patients assessed in the efficacy analysis for all randomized groups.
   E) The number of serious adverse events, deaths, number of withdrawals due to adverse events in each group, reasons for withdrawal for all randomized groups.

2. A systematic review of cross-over trials should be conducted to complement the findings of this systematic review.
3. Further systematic reviews can be conducted to answer other clinically relevant questions that are closely related to this review:

3.1 What is the additional BP lowering efficacy of thiazides in patients who did not respond to monotherapy with another class of antihypertensive drug? This question would be limited to non-responders to monotherapy.

3.2 What is the additional BP lowering efficacy of thiazides given in combination beyond 12 weeks of treatment?

3.3 Is there a difference in the BP lowering efficacy of different drug combinations involving diuretics? A systematic review of clinical trials with head-to-head comparisons of thiazides with different drug classes should be performed in order to determine if there is a difference in BP reduction achieved with different regimens.

4. A systematic review of the adverse effects of combination therapy should be performed to investigate the rate and severity of adverse events in long-term trials.

5. Long-term trials of head-to-head comparisons of different drug combinations must be performed in order to determine whether there are class-specific effects on morbidity and mortality, which are not dependent on their BP lowering effect.
APPENDICES

Appendix A – Search strategy

Search strategy used for MEDLINE

1. randomized controlled trial$.mp
2. randomized controlled trial.pt
3. controlled clinical trial.pt
4. controlled clinical trial$.mp
5. random allocation.mp
6. exp random allocation/
7. exp double-blind method/
8. double-blind.mp
9. exp single-blind method/
10. single-blind.mp
11. or/1-10
12. (animals not human).sh
13. 11 not 12
14. clinical trial$.mp
15. clinical trial.pt
16. (clin$ adj25 trial$).mp
17. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp
18. random$.mp
19. exp research design/
20. research design.mp
21. or/14-20
22. 21 not 12
23. 13 or 22
24. comparative stud$.mp
25. evaluation stud$.mp
26. follow up stud$.mp
27. prospective stud$.mp
28. (control$ or prospective$ or volunteer$).mp
29. or/24-28
30. 29 not 12
31. 23 or 30
32. blood pressure.mp
33. exp hypertension/
34. hypertens$.mp
35. exp blood pressure/
36. or/32-35
37. 31 and 36
38. amlodipine.mp
39. aranidipine.mp
40. azelnidipine.mp
41. barnidipine.mp
42. bencyclane.mp
43. benidipine.mp
44. bepridil.mp
45. cilnidipine.mp
46. cinnarizine.mp
47. clentiazem.mp
48. darodipine.mp
49. diltiazem.mp
50. efonidipine.mp
51. elgodipine.mp
52. etafenone.mp
53. fantofarone.mp
54. felodipine.mp
55. fendiline.mp
56. flunarizine.mp
57. gallopamil.mp
58. isradipine.mp
59. lacidipine.mp
60. lidoflazine.mp
61. lomerizine.mp
62. manidipine.mp
63. mibefradil.mp
64. nicardipine.mp
65. nifedipine.mp
66. niguldipine.mp
67. nilvadipine.mp
68. nimodipine.mp
69. nisoldipine.mp
70. nitrendipine.mp
71. perhexiline.mp
72. prenylamine.mp
73. semotiadil.mp
74. terodiline.mp
75. tiapamil.mp
76. verapamil.mp
77. calcium channel blocker$.mp
78. calcium channel antagonist$.mp
79. or/38-78
80. furosemide.mp
81. bumetanide.mp
82. piretanide.mp
83. torasemide.mp
84. azosemide.mp
85. ethacrynic acid.mp
86. ticrynafen.mp
87. tripamide.mp
88. phenoxybenzoic acid.mp
89. muzolimine.mp
90. indacrinone.mp
91. etozolin.mp
92. ozolinone.mp
93. cicletanine.mp
94. cicletanine.mp
95. tienilic acid.mp
96. tizolemid.ep
97. hydrochlorothiazide.mp
98. chlorothiazide.mp
99. buthiazide.mp
100. bendroflumethiazide.mp
101. hydroflumethiazide.mp
102. trichlormethiazide.mp
103. methylclothiazide.mp
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107. chlorthalidone.mp
108. metolazone.mp
109. quinethazone.mp
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111. clorexolone.mp
112. clopamide.mp
113. indapamide.mp
114. diapamide.mp
115. isodapamide.mp
116. mefruside.mp
117. xipamide.mp
118. diuretic$.mp.
119. or/80-118
120. ace inhibitor$.mp
121. angiotensin-converting enzyme inhibitor$.mp
122. exp angiotensin-converting enzyme inhibitor/
123. exp ace inhibitor/
124. alacepril.mp
125. altiopril.mp
126. benazepril.mp
127. captopril.mp
128. ceronapril.mp
129. cilazapril.mp
130. delapril.mp
131. derapril.mp
132. enalapril.mp
133. fosinopril.mp
134. idapril.mp
135. imidapril.mp
136. lisinopril.mp
137. moexipril.mp
138. moveltipril.mp
139. pentopril.mp
140. perindopril.mp
141. quinapril.mp
142. ramipril.mp
143. spirapril.mp
144. temocapril.mp
145. trandolapril.mp
146. zofenopril.mp
147. or/120-146
148. angiotensin receptor blocker$.mp
149. candesartan.mp
150. eprosartan.mp
151. irbesartan.mp
152. losartan.mp
153. telmisartan.mp
154. tasosartan.mp
155. valsartan.mp
156. or/148-155
157. exp beta-agonist/
158. exp beta-blocker/
159. beta blocker$.mp
160. beta-antagonist$.mp
161. acebutolol.mp
162. alprenolol.mp
163. amosulalol.mp
164. arotinolol.mp
165. atenolol.mp
166. befunolol.mp
167. betaxolol.mp
168. bevantolol.mp
169. bisoprolol.mp
170. bopindolol.mp
171. bocumolol.mp
172. bofetolol.mp
173. bofuralol.mp
174. bunitrolol.mp
175. bupranolol.mp
176. butofilolol.mp
177. carazolol.mp
178. carteolol.mp
179. carvedilol.mp
180. celiprolol.mp
181. cetamolol.mp
182. cloranolol.mp
183. dilevalol.mp
184. epanolol.mp
185. esmolol.mp
186. idenolol.mp
187. labetolol.mp
188. levobunolol.mp
189. mepindolol.mp
190. metipranolol.mp
191. metoprolol.mp
192. moprolol.mp
193. nadolol.mp
194. nadoxolol.mp
195. nebivalol.mp
196. nifenalol.mp
197. oxprenolol.mp
198. penbutolol.mp
199. pindolol.mp
200. practolol.mp
201. pronethalol.mp
202. propranolol.mp
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204. sulfinalol.mp
205. talinolol.mp
206. tertatolol.mp
207. timolol.mp
208. toliprolol.mp
209. xibenolol.mp
210. or/157-209
211. guanabenz.mp
212. rilmemidine.mp
213. clonidine.mp
214. moxonidine.mp
215. methyldopa.mp
216. guanfacine.mp
217. or/211-216
218. renin inhibitor$.mp
219. aliskiren.mp
220. remikiren.mp
221. or/218-220
222. 79 and (119 or 147 or 156 or 210 or 217 or 221)
223. 119 and (147 or 156 or 210 or 217 or 221)
224. 147 and (156 or 210 or 217 or 221)
225. 156 and (210 or 217 or 221)
226. 210 and (217 or 221)
227. 217 and 221
Search strategy used for EMBASE

1. randomized controlled trial$.mp
2. controlled clinical trials.mp
3. exp controlled clinical trial/
4. random allocation.mp.
5. exp random allocation/
6. double-blind.mp
7. single-blind.mp
8. or/1-7
9. exp animal/
10. 8 not 9
11. clinical trial$.mp
12. exp clinical trials/
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. 10 or 19
21. comparative stud$.mp
22. exp comparative study/
23. exp evaluation studies/
24. evaluation stud$.mp
25. follow up stud$.mp
26. exp follow up studies/
27. prospective stud$.mp
28. (control$ or prospective$ or volunteer$).mp
29. or/21-28
30. 29 not 9
31. 20 or 30
32. blood pressure.mp
33. exp hypertension/
34. hypertens$.mp
35. exp blood pressure/
36. or/32-35
37. 31 and 36
38. amlodipine.mp
39. aranidipine.mp
40. azelnidipine.mp
41. barnidipine.mp
42. bencyclane.mp
43. benidipine.mp
44. bepridil.mp
45. cilnidipine.mp
46. cinnarizine.mp
47. clentiazem.mp
48. darodipine.mp
49. diltiazem.mp
50. efonidipine.mp
51. elgodipine.mp
52. etafenone.mp
53. fantofarone.mp
54. felodipine.mp
55. fendiline.mp
56. flunarizine.mp
57. gallopamil.mp
58. isradipine.mp
59. lacidipine.mp
60. lidoflazine.mp
61. lomerizine.mp
62. manidipine.mp
63. mibefradil.mp
64. nicardipine.mp
65. nifedipine.mp
66. niguldipine.mp
67. nilvadipine.mp
68. nimodipine.mp
69. nisoldipine.mp
70. nitrendipine.mp
71. perhexiline.mp
72. prenylamine.mp
73. semotiadil.mp
74. terodiline.mp
75. tiapamil.mp
76. verapamil.mp
77. calcium channel blocker$.mp
78. exp calcium channel blocker/
79. calcium channel antagonist$.mp
80. exp calcium channel antagonist/
81. or/38-80
82. furosemide.mp
83. bumetanide.mp
84. piretanide.mp
85. torasemide.mp
86. azosemide.mp
87. ethacrynic acid.mp
88. ticrynafen.mp
89. tripamide.mp
90. phenoxybenzoic acid.mp
91. muzolimine.mp
92. indacrinone.mp
93. etozolin.mp
94. ozolinone.mp
95. cicletanine.mp
96. cicletanine.mp
97. tienilic acid.mp
98. tizolemide.mp
99. hydrochlorothiazide.mp
100. chlorothiazide.mp
101. buthiazide.mp
102. bendroflumethiazide.mp
103. hydroflumethiazide.mp
104. trichlormethiazide.mp
105. methylclothiazide.mp
106. polythiazide.mp
107. cyclothiazide.mp
108. cyclopenthiazide.mp
109. chlorthalidone.mp
110. metolazone.mp
111. quinethazone.mp
112. fenquizone.mp
113. clorexolone.mp
114. clopamide.mp
115. indapamide.mp
116. diapamide.mp
117. isodapamide.mp
118. mefruside.mp
119. xipamide.mp
120. diuretic$.mp.
121. exp diuretic/
122. or/82-121
123. ace inhibitor$.mp
124. angiotensin-converting enzyme inhibitor$.mp
125. exp angiotensin-converting enzyme inhibitor/
126. exp ace inhibitor/
127. alacepril.mp
128. altiopril.mp
129. benazepril.mp
130. captopril.mp
131. ceronapril.mp
132. cilazapril.mp
133. delapril.mp
134. derapril.mp
135. enalapril.mp
136. fosinopril.mp
137. idapril.mp
138. imidapril.mp
139. lisinopril.mp
140. moexipril.mp
141. moveltipril.mp
142. pentopril.mp
143. perindopril.mp
144. quinapril.mp
145. ramipril.mp
146. spirapril.mp
147. temocapril.mp
148. trandolapril.mp
149. zofenopril.mp
150. or/123-149
151. angiotensin receptor blocker$.mp
152. candesartan.mp
153. eprosartan.mp
154. irbesartan.mp
155. losartan.mp
156. telmisartan.mp
157. tasosartan.mp
158. valsartan.mp
159. or/151-158
160. exp beta-antagonist/
161. exp beta-blocker/
162. beta blocker$.mp
163. beta-antagonist$.mp
164. acebutolol.mp
165. alprenolol.mp
166. amosulalol.mp
167. arotinolol.mp
168. atenolol.mp
169. befunolol.mp
170. betaxolol.mp
171. bevantolol.mp
172. bisoprolol.mp
173. bopindolol.mp
174. bocumolol.mp
175. bofetolol.mp
176. bofuralol.mp
177. bunitrolol.mp
178. bupranolol.mp
179. butofilolol.mp
180. carazolol.mp
181. carteolol.mp
182. carvedilol.mp
183. celiprolol.mp
184. cetamolol.mp
185. cloranolol.mp
186. dilevalol.mp
187. epanolol.mp
188. esmolol.mp
189. idenolol.mp
190. labetolol.mp
191. levobunolol.mp
192. mepindolol.mp
193. metipranolol.mp
194. metoprolol.mp
195. moprolol.mp
196. nadolol.mp
197. nadoxolol.mp
198. nebivalol.mp
199. nifenalol.mp
200. oxprenolol.mp
201. penbutolol.mp
202. pindolol.mp
203. practolol.mp
204. pronethalol.mp
205. propranolol.mp
206. sotalol.mp
207. sulfinalol.mp
208. talinolol.mp
209. tertatolol.mp
210. timolol.mp
211. toliprolol.mp
212. xibenolol.mp
213. or/160-212
214. guanabenz.mp
215. rilmemidine.mp
216. clonidine.mp
217. moxonidine.mp
218. methyldopa.mp
219. guanfacine.mp
220. or/214-219
221. renin inhibitor$.mp
222. exp renin inhibitor/
223. aliskiren.mp
224. remikiren.mp
225. or/221-224
226. 81 and (122 or 150 or 159 or 213 or 220 or 225)
227. 122 and (150 or 159 or 213 or 220 or 225)
228. 150 and (159 or 213 or 220 or 225)
229. 159 and (213 or 220 or 225)
230. 213 and (220 or 225)
231. 220 and 225
232. or/226-231
233. 37 and 232
Appendix B – Methological graph

Adequate sequence generation?  Yes (low risk of bias)
Allocation concealment?  Yes (low risk of bias)
Blinding?  Yes (low risk of bias)
Incomplete outcome data addressed?  Yes (low risk of bias)
Free of selective reporting?  Yes (low risk of bias)