A SYSTEMATIC REVIEW OF THE BLOOD PRESSURE LOWERING EFFICACY OF THIAZIDE AND LOOP DIURETICS IN THE TREATMENT OF PRIMARY HYPERTENSION

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES
Department of Pharmacology and Therapeutics
Faculty of Medicine

We accept this thesis as conforming to the required standard

The University of British Columbia
April 2000
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Date 25th April 2000
ABSTRACT

Context.- First-line treatment of hypertension with low- or high-dose thiazide therapy compared to placebo or untreated control group reduced blood pressure to a similar extent but their effect on mortality or coronary events appeared to be different.

Objectives.- To determine the dose-related decrease in systolic and diastolic blood pressure, withdrawal due to adverse drug effects and metabolic adverse effects of thiazide and loop diuretic monotherapy compared to a placebo control, for a duration of 3-12 weeks, in patients with primary hypertension (SBP ≥ 160 and/or DBP ≥ 90 mmHg).

Design.- A systematic review of all randomised placebo controlled trials.

Setting.- Electronic databases were searched using the standard search strategy of the Cochrane Hypertension Review group. Data were analysed using Review Manager 4.0.

Participants.- 33 trials, involving 4,811 patients reported data on thiazides and only 3 trials involving 150 patients reported data on loop diuretics.

Results.- BP lowering efficacy: The dose of thiazide approaching near maximal systolic and diastolic blood pressure lowering efficacy with the best overall estimate in mm Hg identified was: hydrochlorothiazide 25 mg/day (9/5); chlorthalidone 12.5 mg/day (10/3) and indapamide 1.0 mg/day (7/4). The overall best estimate for combined doses of all thiazide drugs was 10/4 mm Hg. Low- and high-dose thiazides lowered blood pressure to a similar extent.
Evidence relating to loop diuretics is insufficient to determine a dose-related effect on any of the outcome measures.

Withdrawal due to adverse drug effects were similar to the placebo group in low and high-dose thiazide trials. The overall relative risk of withdrawal due to adverse events for thiazides was 1.2(0.8, 1.2).

Metabolic adverse effects: Combined high doses of all thiazide drugs showed a significant decrease in serum potassium levels as compared to combined low-doses. A significant decrease in serum potassium and a significant increase in serum uric acid, creatinine, triglyceride and total cholesterol were observed compared to the placebo control group.

Conclusion.- The lowest range of clinically used doses of thiazide diuretic showed near maximal blood pressure lowering efficacy and a lower incidence of adverse metabolic effects. It is recommended that there is no advantage to using doses higher than those defined as low dose.
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ACKNOWLEDGEMENTS

I wish to thank Dr. James M. Wright, my supervisor, for his unconditional support throughout this thesis work. He was always available for advice despite his many other duties. His interest, patience, guidance and encouragement helped me complete my thesis in such a short time and with so much fun.

I would also specially like to thank Dr. Ken Bassett, for teaching me how to critically appraise research trials. His support and constructive criticism has always been a source of encouragement for me to strive for excellence.

I am deeply appreciative of my committee members, Drs. David Godin and Robert Rangno for their support, encouragement, valuable comments and criticism.

I am grateful to Stephen Adams for retrieving innumerable articles from the library for this systematic review. This project would not have been possible without his help. I am also grateful to Amit Ahuja for being the second independent reviewer.

I would like to thank Mr. Ciprian Jauca and other members of the Therapeutics Initiative and the Department of Pharmacology and Therapeutics, for being so nice to me. I am grateful to Mrs. Wynne Leung for her superb assistance in the computer portion of my work.

Last but not the least, I would like to thank my sisters Jyoti, Vanita, Seema and Geeta who showed me the meaning of team work, unconditional love, support and trust. I am also thankful to my friends Mrs. Jayashree Rana and Dr. R. D. Begamudre for their valuable comments on the manuscript.
DEDICATION

Dedicated to

MY PARENTS

Vaman Ramchandra Balgi and Seeta Vaman Balgi

for the uncompromising principles that guided their life,

for leading their children into intellectual pursuits and

for their unconditional love, wisdom and patience

MY HUSBAND

Manavendra Musini

for his love, infinite patience and support

and

MY CHILDREN

Neha and Manmadh

for making life worthwhile and giving a meaning to everything I do.
1. BACKGROUND INFORMATION

1.1. Hypertension

Hypertension is one of the most prevalent cardiovascular risk factor found in the developed world. Despite differences in hypertension definition and measurement methods, the reported prevalence of hypertension (using the arbitrary level of 140/90 mm Hg) ranges about 20% across adult populations. Because of its association with increased incidence of atherosclerotic heart disease and stroke, hypertension is an important public health problem in virtually all areas of the world where blood pressure (BP) is measured.¹

1.1.1. Definition of hypertension

The prevailing confusion as to the criteria for diagnosing hypertension may be attributed to the fact that there is still no universally recognised definition of this condition. There is a continuous, direct relationship between BP and increased risk of stroke, heart failure, renal disease, peripheral vascular disease and coronary artery disease including myocardial infarction and sudden death.² Therefore, the dividing line between “normotension” and “hypertension” based on the values of pressure is arbitrary. Although arbitrary, selecting cut-off values allows researchers to quantify both the potential risk of complications of hypertension and the benefits of therapy in large populations.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are strongly correlated, but they may provide independent relevant clinical information.³ SBP can be measured with greater precision than DBP. Observation from the long term Framingham cohort study found SBP was a better predictor of coronary heart disease (CHD) than DBP. In the same study, DBP gave a better estimate of the mean blood
pressure (MBP) and was a stronger predictor of the risk of hemorrhagic stroke. Both SBP and DBP were significant predictors of thrombo-embolic brain infarction.\textsuperscript{4} The prognostic heterogeneity of SBP and DBP implies that both should be considered in clinical care.

Epidemiological studies have found that increased cardiovascular risk is associated with even a modest elevation of DBP 80-89 mm Hg or SBP 120-139 mm Hg.\textsuperscript{2} For example, individuals with DBP of 105 mm Hg have a tenfold increase in the relative risk of stroke and a fivefold increase in risk of coronary heart disease (CHD) compared with those with DBP of 76 mm Hg.\textsuperscript{5}

Clinical trials also conclude a strong predictive value between SBP and significant clinical events. In addition, SBP has been associated with a higher relative risk of cardiovascular events. In the MRFIT trial for example, the relative risk of CHD increased from 1.0 in individuals with SBP less than 120 mm Hg to 4.2 in individuals with SBP greater than 160 mm Hg.\textsuperscript{6}

Not surprisingly, different guideline committees recommend different level of SBP and DBP to establish a diagnosis of hypertension. The World Health Organisation (WHO) and International Society of Hypertension (ISH) guidelines committee have agreed to adopt, in principle, the definition and classification provided in Joint National Committee (JNC VI). That committee defined hypertension as a SBP of 140 mm Hg or greater and/or DBP of 90mm Hg or greater in subjects who are not taking antihypertensive medication.\textsuperscript{7}

Alternatively, a clinical definition of hypertension, need not be based solely on arbitrary blood pressure levels but include the benefit to harm ratio of a therapeutic agents. Professor Geoffrey Rose states hypertension is “that level of blood pressure
above which investigation and treatment do more good than harm". It is therefore essential to evaluate the benefits and harm of antihypertensive investigation and pharmacotherapy in randomised controlled trials to better understand the level of BP at which investigation and treatment do provides more benefit than harm. This level of SBP and DBP will be discussed in further detail in section 1.1.7. ‘Benefits of treatment’.

1.1.2. High BP in relation to cardiovascular risk factors

Cardiovascular disease is associated with many risk factors, one of which is the level of blood pressure - the higher the blood pressure the higher the risk of both stroke and coronary vascular events. Other risk factors for cardiovascular disease are: (increasing) age, male gender, previous history of cardiovascular events, target organ damage (left ventricular failure), renal disease, smoking, diabetes, hyperlipidemia, central obesity and sedentary life style.

The Framingham data demonstrate that the presence of glucose intolerance, hyperlipidemia, cigarette smoking and left ventricular hypertrophy confer an exponentially increased risk of cardiovascular disease in patients, particularly men. Thus, the management of hypertension needs to take into account other cardiovascular risk factors as well.

1.1.3. Goals of treatment in patients with high blood pressure

Lowering BP is a surrogate outcome and the best way to assess the benefits of therapy is to evaluate the impact on the clinically relevant outcomes, mortality and cardiovascular morbidity. Therefore, the primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the total cardiovascular morbidity and mortality. This requires evidence that the specific treatment works to
reduce cardiovascular morbidity and mortality and treatment of all treatable factors identified.

1.1.4. The management of hypertension

The clinical diagnosis and the factors that need to be considered in the management of hypertension is complex. Diagnosis requires multiple measurements to establish the individual's mean resting BP. Other variables include the method of indirect estimate of BP measurement, threshold BP to initiate treatment, and the target BP to be achieved by treatment.

Precise BP measurement cannot be obtained by one-time single reading. It is known to vary due to day and night rhythms, the type of activity and the emotional state of the subject. The mean of many BP readings permits a more accurate classification of actual BP status than a single reading.\(^3\) Therefore, BP levels should be based on at least three sets of readings over several weeks.\(^{11}\) Several studies have found increasing validity with repeated BP measurements.\(^{12,13}\)

There is additional uncertainty regarding the place of measurement of BP (situational hypertension), relationship between home BP and clinic BP readings, and the role of repeated or ambulatory BP readings over 24 hour period in the clinical management of hypertension.\(^{14-16}\) None of the locations or methods are linked to morbidity or mortality. All guidelines recommend a period of observation of between 3 and 6 months after the initial assessment of BP before a definitive confirmation of the diagnosis of mild-to-moderate hypertension can be made.\(^{12}\)

Debate also continues regarding the threshold BP level to initiate treatment when hypertension is the only risk factor for cardiovascular disease or when other risk factors are present.\(^{19}\) The UK\(^{20}\), New Zealand\(^{21}\) and Canada\(^{22}\) tend to select higher DBP
values to start treatment, with no difference in SBP (DBP threshold 100 mm Hg, SBP threshold 160-170 mm Hg); the WHO/ISH\textsuperscript{14} and Australian\textsuperscript{23} guidelines recommend a DBP threshold of 95 mm Hg and a SBP threshold of 160 mm Hg; and the 5\textsuperscript{th} report of the Joint National Committee (JNC)\textsuperscript{15} in USA recommends a DBP threshold of 90 mm Hg and SBP threshold of 150 mm Hg in the absence of other risk factors. For patients with more than one risk factor, the guidelines are consistent that the threshold for treatment should be 140/90 mm Hg.\textsuperscript{15,22,23}

There is further uncertainty regarding the target BP to be achieved through drug treatment. Researchers have cautioned that excessive lowering of BP causes more harm than good.\textsuperscript{24} However, they have not determined the lowest level of BP after which further lowering no longer results in benefit. There are conflicting findings from randomised controlled trials in this regard. The Hypertension Optimal treatment (HOT) trial\textsuperscript{25} randomised 18,790 patients 50-80 years old, with DBP 100-115 mm Hg to three BP target groups (DBP ≤ 90, 85 or 80 mm Hg). There was no placebo control group in this study. The primary end point was to assess association between major cardiovascular events and target BP during antihypertensive therapy. The primary outcomes in the three target groups were not significantly different from each other. However, there was a trend towards an increased mortality in the lower target groups. This trial answers the question that there is nothing to be gained from lowering BP less than a target of 90 mm Hg. However, it does not indicate whether a higher diastolic target, such as 95-100 mm Hg, would achieve similar outcomes, or whether using systolic targets is a more rational clinical trial design. In a subgroup analysis of diabetic patients in the HOT study, there was a significantly lower risk of cardiovascular disease in those patients assigned to the lowest blood pressure target. This is based on smaller
numbers of events and requires confirmation. It does, however, show that excluding diabetic patients from analysis further suggests a trend towards worse outcomes in the lower BP target groups.

The United Kingdom Prospective Diabetes study (UKPDS) trial\textsuperscript{26} randomised 1148 type 2 diabetic patients with hypertension (defined as SBP $\geq$ 160 mm Hg or DBP $\geq$ 90 mm Hg or SBP $\geq$ 150 mm Hg on no medications or DBP $\geq$ 85 mm Hg in patients taking antihypertensive medication) to either tight control of BP (aiming at 150/85 mm Hg) or less tight control of BP (aiming at $< 180/105$ mm Hg) with a median follow-up of 8.4 years. This study demonstrated that aiming for the target of $< 150/85$ mm Hg conferred a substantial reduction in the risk of major cardiovascular events compared to the higher target. However, it is important to note that the high target control group was essentially an untreated control group. Post-hoc analyses based on mean achieved BP levels are not meaningful, as achieved BP reflects many other factors than the target BP.

1.1.5. Approach to the treatment of hypertension

Hypertension is a chronic heterogeneous disease that is multifactorial origin. One or more pathogenic factors may play a dominant role in any individual. Therefore any drug, whatever its mode of action, may or may not normalise BP only in any group of patients. Hypertension itself is usually asymptomatic, varies with time, place and is usually lower in the second or subsequent visits than the first clinic visit to a physician.\textsuperscript{27} Many patients initially labelled as having elevated BP become normotensive without therapy. Thus, treatment with antihypertensive drug therapy entails careful drug titration both increasing doses and use of additional drugs, as well as decreasing doses and stopping drugs to achieve goal BP levels.
1.1.6. Rationale for reducing elevated BP

Considerable scientific evidence from observational studies conclude that reducing elevated blood pressure is beneficial, particularly in patients with additional cardiovascular risk factors. In addition to reducing morbidity and mortality, treatment helps to prevent the progression of elevated blood pressure. Data of multiple randomised placebo-controlled trials concluded that fewer patients had their hypertension progress from their initially less severe degree to more severe hypertension (BP > 200/110 mm Hg in only 95 of 13,389 patients on active treatment versus 1493 of 13,342 patients on placebo group).

In patients with severe hypertension, the benefit of treatment is obvious. Malignant or accelerated essential hypertension is now an uncommon event. Before modern antihypertensive drugs were introduced, the diagnosis of this form of hypertension fully warranted the description of 'malignant' because approximately 90% of the patients died within 1 year of diagnosis. Treatment with injectable hexamethonium and/or pentolinium brought about a dramatic change in the clinical course of the disease. Renal function played a significant role in the outcome of patients undergoing treatment for malignant hypertension. Patients with preserved renal function at the start of treatment showed prolonged survival whereas patients with significant renal failure at the time of the diagnosis showed a high mortality rate in the first year. One of the most dramatic observations of the last 40 years is the marked reduction in the incidence of malignant hypertension.

The scientific evidence of benefit versus harm for treating mild hypertension is small compared to treatment of moderate to severe hypertension. More over the absolute risk of cardiovascular disease in mild hypertension varies from one geographic
region to another. This may be due to regional differences in the prevalence of other cardiovascular disease risk factors. However, other evidence indicates there are some regional differences that cannot be accounted for by the established risk factors. For example, the stroke rate in China and USSR is 4 times that of USA and Western Europe although the average population BP values differ only slightly. For this reason, the treatment of mild hypertension in these populations may yield benefits of greater magnitude.\textsuperscript{32}

It has been shown in randomised controlled trials that on an average 5-6 mm Hg reduction in DBP and 10 mm reduction in SBP reduces the relative risk of stroke by about a third and the risk of coronary events by about a sixth.\textsuperscript{6} Thus, it seems appropriate to achieve maximum tolerated BP reduction, although there is still no consensus on how far BP should be lowered.\textsuperscript{6} The lowering of BP is commonly accepted as a surrogate outcome for reduction in cardiovascular morbidity and mortality.\textsuperscript{19}

1.1.7. Benefits of treatment

Clinical trials designed to study the benefits of BP reduction with respect to total mortality and clinical events in hypertensive patients have demonstrated that treatment of middle-aged and elderly (> 65 years) hypertensive patients reduces the incidence of cerebrovascular and cardiovascular events.\textsuperscript{33}

Antihypertensive treatment has been less effective in preventing coronary heart disease (CHD).\textsuperscript{34} It is not clear whether this is due to inadequate BP control, inadequate intervention of other risk factors, negative effects on the risk of cardiovascular disease from antihypertensive drugs, intervention being too late to affect atherosclerosis, or inadequate effects of present drugs on atherosclerosis or different
pathophysiologic processes in different perfusion beds.\textsuperscript{35} Despite treatment for 20-22 years, treated hypertensive men have a significantly increased mortality from CHD, compared with non-hypertensive men from the same population.\textsuperscript{36}

Seventeen randomised controlled trials have evaluated all cause mortality and cardiovascular specific morbidity in patients with varying degrees of hypertension, treated with multiple drug therapy for at least one year duration. The benefits of treatment in each individual trial, however, depended on sample size, power of the trial to detect a difference, the inclusion/exclusion criteria, the withdrawal rate, compliance with therapy and the extent to which SBP and DBP were lowered.

Eleven of the seventeen trials had patients with moderate to severe elevation of BP (defined as mean baseline SBP 160 mm Hg or more and/or DBP 114 mm Hg or more), (HSCSG\textsuperscript{37}, Kuramoto\textsuperscript{38}, VA I\textsuperscript{39}, VA II\textsuperscript{40}, EWPHBE\textsuperscript{41}, MRC-O\textsuperscript{42}, MRC-TMH\textsuperscript{43}, SHEP-P\textsuperscript{44}, SHEP\textsuperscript{45}, Wolff\textsuperscript{46} et al, and SYST-EUR\textsuperscript{47} trial). Four of the eleven trials (EWPHBE\textsuperscript{41}, SHEP-P\textsuperscript{44}, HSCSG\textsuperscript{37} and Kuramoto\textsuperscript{38} et al) did not show a significant decrease in total mortality or total cardiovascular events. The remaining seven trials did not show a significant decrease in total mortality as well as a significant decrease in total cardiovascular events (relative risk ranging from 0.09 to 0.80 as compared to untreated control group). In the same trials, the decrease in SBP ranged from 14.4 to 36.2 mm Hg and the decrease in the DBP ranged from 5.0 to 27.5 mm Hg.

Three of the seventeen trials had patients with mild elevation of BP defined as mean baseline SBP less than 160 mm Hg and DBP less than 114 mm Hg (USPHSHSG\textsuperscript{48}, ATTMH\textsuperscript{49}, and Oslo study\textsuperscript{50}). These trials showed no significant decrease in total mortality or total cardiovascular events.
The remaining three of the seventeen trials (Barraclough\textsuperscript{51} et al, Carter\textsuperscript{52} et al and VA-NHLBI\textsuperscript{53}) did not report the mean baseline SBP/DBP levels and therefore could not be classified.

\textbf{1.1.8. Treatment of hypertension}

Non-pharmacological adjuncts to therapy should be considered routinely in the treatment of hypertension. The usual recommendations are to modify their lifestyle, stopping smoking, weight reduction, limiting intake of alcohol and dietary saturated fat and engaging in regular mild dynamic exercise. Salt restriction may assist in lowering blood pressure. The magnitude of BP reduction with non-pharmacological measures is 10-15mm Hg SBP and 6-10mm Hg DBP.\textsuperscript{54} 20-25\% of mild hypertensives become normotensive with non-pharmacological intervention. Thus non-pharmacological therapies can produce persistent, clinically significant reduction in BP of the same magnitude as those resulting from drug therapy.\textsuperscript{55}

\textbf{Pharmacotherapy of hypertension:}

Several antihypertensive drugs from different drug classes have become available during the last 70 years.\textsuperscript{56}
Table 1: Introduction of antihypertensive treatment

<table>
<thead>
<tr>
<th>Decade</th>
<th>Class</th>
<th>Representative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930s</td>
<td>Veratrum alkaloids,</td>
<td>Hexamethonium</td>
</tr>
<tr>
<td></td>
<td>Veratrum alkaloids,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mercurial diuretics</td>
<td>Mecamylamine, pentolium</td>
</tr>
<tr>
<td>1940s</td>
<td>Thiocynates,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganglion blocking agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hexamethonium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mecamylamine, pentolium</td>
<td></td>
</tr>
<tr>
<td>1950s</td>
<td>Vasodilators,</td>
<td>Hydralazine</td>
</tr>
<tr>
<td></td>
<td>Rauwolfia alkaloids</td>
<td></td>
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<tr>
<td></td>
<td>Peripheral sympathetic inhibitors</td>
<td>Reserpine</td>
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<tr>
<td></td>
<td>Diuretics</td>
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<tr>
<td></td>
<td>Guanethidine,</td>
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<tr>
<td></td>
<td>Chlorthiazide,</td>
<td></td>
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<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td></td>
</tr>
<tr>
<td>1960s</td>
<td>Central sympathetic inhibitors</td>
<td>Alpha methylidopa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonidine, Guanabenz</td>
</tr>
<tr>
<td></td>
<td>Beta-adrenergic blocking agents</td>
<td>Propranolol</td>
</tr>
<tr>
<td>1970s</td>
<td>Alpha-adrenergic blocking agents</td>
<td>Prazosin</td>
</tr>
<tr>
<td></td>
<td>ACE Inhibitors</td>
<td>Captopril, Enalapril</td>
</tr>
<tr>
<td>1980s</td>
<td>Calcium antagonists</td>
<td>Dilitazem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nifedipine, Verapamil</td>
</tr>
<tr>
<td>1990s</td>
<td>Angiotensin II blockers</td>
<td>Losartan</td>
</tr>
</tbody>
</table>

An ideal antihypertensive agent for initial therapy should be efficacious as monotherapy, well tolerated, have a convenient dosing schedule, easy to titrate, should have low incidence of pseudotolerance (vasodilator - fluid retention), and if needed should augment the action of other antihypertensive agents added later. It should also be inexpensive.
1.1.9. The relationship between blood pressure and clinical events

There is considerable scientific evidence that equal reductions of BP by different antihypertensive agents does not necessarily have equal benefit in terms of preventing cardiovascular events. Antihypertensive drug therapy therefore should be based on the evidence of reduction in mortality and cardiovascular and cerebrovascular morbidity and not simply reduction in BP.

A systematic review by Wright et al 1999 of first-line antihypertensive therapy (including diuretics, beta-blockers, calcium-channel blockers, alpha-adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) demonstrated that diuretics significantly decreased the incidence of mortality, stroke, coronary heart disease and total cardiovascular events compared to placebo or untreated control group. Beta-blocker drug therapy had no statistically significant benefit on any of these primary outcome measures. Calcium-channel blocker drug therapy significantly reduced the risk of stroke and total cardiovascular events in one trial but had no statistically significant effect on mortality or coronary heart disease as compared to an untreated control group. Data are lacking about the effectiveness of alpha-adrenergic blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. The diuretics used as first-line treatment of hypertension were hydrochlorothiazide, bendroflumethiazide, chlorthiazide, methylclothiazide, trichlormethiazide and chlorothalidone. This systematic review also demonstrated that the SBP lowering efficacy of thiazide at one year was significantly more by 5-6 mm Hg than beta-blocker or calcium channel blocker drug therapy. The DBP lowering efficacy was similar for these three drug classes.
1.1.10. Aim of this systematic review

Thiazide diuretics are the only class of first-line antihypertensive drugs that have evidence of proven effectiveness in terms of significant reduction in all cause mortality as well as cardiovascular morbidity. It is therefore important to know their BP lowering dose-response effects. Loop diuretics have not been studied as first-line agents for their ability to reduce morbidity and mortality. Non-diuretic doses of loop diuretics are known to lower BP but their BP lowering dose-response effect is not known. Therefore, the main aim of this systematic review is to determine the BP lowering dose-response effect of both thiazide and loop diuretics in the treatment of primary hypertension. The secondary outcomes which will also be examined are dose-related withdrawal due to adverse drug effects and dose-related metabolic adverse events.

This review may help to determine the dose-response relationship for the BP lowering and adverse effects for each diuretic. In this way, it may be possible to determine the dose of diuretic which maximises the BP lowering effect while minimising the adverse effects.

1.2. Diuretics

Antihypertensive drug therapy has been classified according to their anatomical site of action or pharmacologic mechanism of action. In keeping with the former classification, the drugs acting on the kidneys have been further classified as ‘thiazide or thiazide class of diuretics’ (acting on the distal convoluted tubule), as ‘loop diuretics’ (acting on the ascending limb of the loop of Henle) and as ‘potassium sparing diuretic’ (acting on the late distal tubule and the collecting duct). This systematic review is limited only to thiazide and loop diuretics.58
Thiazides are benzothiadizines. Chlorthiazide was the first drug developed. A number of oral diuretics were developed that had an aryl-sulphonamide structure and blocked the sodium-potassium-chloride co-transporter. Some of these agents are not benzothiadizines, but because they have structural features and molecular actions, similar to the original benzothiadizine compounds, they are designated as members of the ‘thiazide class of diuretics’. For example cholorthalidone and indapamide are non-benzothiadizine in the ‘thiazide class of diuretics’.

Further molecular modification in the 1960s led to the compounds furosemide and bumetanide. These agents, although also sulfonamide derivatives, have very few chemical features in common with thiazides. Their mechanism of action is similar to that of ethacrynic acid (which act on the loop of Henle) but different from that of thiazides (which act on the distal convoluted tubule).

1.2.1. Mechanism of action of diuretics in general

The exact mechanism of the action of diuretics to lower BP is not yet certain. They are known to alter the sodium balance. When used in the treatment of hypertension, their early effect was to decrease extracellular volume, decrease plasma volume and cardiac output and leave peripheral resistance relatively unchanged. After several weeks, the cardiac output returned to normal and the total peripheral resistance decreased. 57, 58

Diuretics' mechanism of BP lowering action through the kidney is suggested by the fact that anephric patients and nephrectomized animals do not show a reduction in BP when given thiazide diuretics. In addition, high salt intake, or infusion of saline, to counteract the net negative sodium balance produced by different diuretics reverses the antihypertensive effect. During effective therapy, the plasma volume remains about 5%
below the pre-treatment values; plasma renin activity remains elevated, suggesting the persistent reduction in body sodium.\textsuperscript{58-61}

Diuretics mechanism of action on smooth muscles of the vasculature was initially thought to be direct and independent of the saluretic effect. However, the fact that BP is not lowered in anephric patients or nephrectomized animals is evidence against that hypothesis. In some experiments, they do relax human vascular smooth muscle \textit{in vitro}. The hemodynamic effects of diuretics to reduce vascular resistance are also produced by restriction of salt. Several possible mechanisms are offered for the reduction of vascular resistance by a persistent, albeit small, reduction in body sodium. These include a decrease in interstitial fluid volume, a fall in smooth muscle sodium concentration that may secondarily reduce intracellular calcium concentration, such that cells are more resistant to contractile stimuli. This causes a change in affinity and response of cell surface receptors to vasoconstrictor hormones. Other mechanisms of action proposed are: the diuretic-induced increase in production of endogenous vasodilators (prostacyclin, PGE2 and kinins); increase in venous capacitance; and reduced endogenous secretion of natriuretic factors that are also vasoconstrictors due to improved natriuresis.\textsuperscript{58-61}

\textbf{1.2.2. Diuretics acting on early distal tubule}

Diuretics acting on the early distal convoluted tubule include thiazides and others in the 'thiazide class' of drugs. The most commonly used thiazide diuretic in North America is hydrochlorothiazide (HCTZ). Others are bendroflumethiazide (BDFZ), chlorthalidone (CTHD), indapamide (IND), cyclopenthiazide (CYPTZ), and metolazone (MTZ).
1.2.2.1. Mechanism of action of thiazide and ‘thiazide class’ diuretics

These drugs have a moderately powerful diuretic action. They decrease active reabsorption of sodium and accompanying chloride by binding to the chloride site of the electroneutral Na/Cl co-transport system and by inhibiting its action. They do not have any action on the loop of Henle. Potassium and magnesium loss with these drugs occurs as a result of the distal tubule sodium exchange and can be significant. Excretion of uric acid and calcium is decreased. They have some extra-renal actions - they produce vasodilation and may transiently increase blood glucose especially in patients with type-2 diabetes, by reducing insulin release. Diazoxide, a non-diuretic thiazide, has powerful vasodilator effects and can also substantially increases blood sugar.

Picckers et al, demonstrated a dose-dependent direct vasodilator effect of hydrochlorothiazide in animal and human isolated resistance arteries at therapeutically relevant concentrations. The mechanism of action was dependent on the activation of vascular potassium channels, which could be blocked by tetraethylammonium (TEA), charybdotoxin, and iberiotoxin. This effect is independent of its renal effect. In patients with Gitelman syndrome characterised by the absence of thiazide sensitive Na-Cl co-transporter, a similar effect of hydrochlorothiazide was seen as compared to controls. Therefore, Na-Cl co-transporters may not play an important role in the BP lowering effect. Whether this direct vasodilator effect contributes to BP lowering is not known. Vasodilation in vivo was only achieved at plasma concentrations of HCTZ that are higher than those normally reached during long term oral treatment. However, both HCTZ and indapamide are known to accumulate in vascular smooth muscle cells and the antihypertensive action of HCTZ is slow in onset and offset. Efficacy of
hydrochlorothiazide may be explained by the combination effect of a small vasodilator action and prevention of the normal counter-regulatory effects by diuresis. *In-vitro* experiments with animal tissue have shown that indapamide acts on vascular smooth muscle by inhibiting the slow inward calcium current. 62

Metabolic side effects lead to some of the known effects of thiazides - decrease in potassium, metabolic alkalosis, increase in plasma uric acid. Unwanted side effects not related to the main renal actions include an increase in plasma cholesterol, male impotence and hypersensitivity reactions. 63

1.2.2.2. Pharmacokinetics of thiazide and ‘thiazide class’ diuretics

The thiazides and related drugs are all effective orally, being well absorbed from the gastrointestinal tract. All are excreted in the urine mainly by tubular secretion. With the shorter acting drugs such as bendroflumethiazide, hydrochlorothiazide, chlorthiazide and cyclothiazide, the onset of action is within 12 hours, the maximum effect is at about 4-6 hours and duration is between 8-12 hours. The longer acting drugs such as chlorthalidone have a similar onset of action but a longer duration of action lasting for more than 24 hours. 58

1.2.3. Loop diuretics

This class of drugs includes furosemide, bumetanide, piretanide, torasemide and ethacrynic acid.

1.2.3.1. Mechanism of action of loop diuretics

Loop diuretics are the most powerful of all known diuretics, capable of causing 15-25% of filtered sodium to be excreted; thus, they are termed ‘high ceiling’ diuretics. These drugs primarily act on the ascending loop of Henle, inhibiting the transport of
sodium chloride out of the tubule into the interstitial tissue by inhibiting Na/K/2Cl carrier in the luminal membrane. Furosemide and bumetanide have a direct inhibiting effect on the carrier, acting on the chloride binding site. Ethacrynic acid forms a complex with cysteine, the complex being the active form of the drug.\textsuperscript{58, 60}

The action of loop diuretics results in more solute being delivered to the distal portion of the nephron where its osmotic pressure further reduces water reabsorption. As much as 25% of the glomerular filtrate may pass out of the nephron compared to the normal loss of 1%, resulting in pressure diuresis. Loop diuretics also have a venodilation action, directly and/or indirectly through the release of a renal factor. Loop diuretics may produce metabolic alkalosis due to the loss of sodium and chloride (with resultant volume depletion), along with potassium depletion and increased hydrogen ion secretion. Loop diuretics increase excretion of calcium and magnesium and decrease excretion of uric acid.

\textbf{1.2.3.2. Pharmacokinetics of loop diuretics}\textsuperscript{64}

The loop diuretics are readily absorbed (furosemide absorption is highly variable) from the gastrointestinal tract and can also be given by injection. They bind strongly to plasma proteins and so do not pass into the glomerular filtrate to any marked degree. They reach their site of action - the luminal surface of the cells of the thick ascending loop by being secreted in the proximal convoluted tubule, by the organic acid transport mechanism. The fraction thus secreted passes out in the urine.\textsuperscript{58}

A fraction of loop diuretic that is not secreted is metabolised by the liver - bumetanide and torasemide being metabolised by cytochrome P-450 pathways and furosemide being glucuronidated. Given orally, they act within one hour; given
intravenously, they produce a peak effect within 30 minutes. The half-lives are about 90 minutes (longer in renal failure) and the duration of action is 3-6 hours.

1.2.4. Importance of diuretics in the treatment of hypertension

Diuretics are the "first step" antihypertensive drugs in the "stepped-care approach". The rationale for their continued use even in non-responders is due to the fact that alternative agents, such as direct vasodilators, centrally acting drugs or sympatholytics, all produce sodium retention, which reduces their antihypertensive effectiveness. The fact that many effective antihypertensive agents reduce BP further when added to thiazides reconfirms their central place in the pharmacological management of hypertension.

Initially, thiazides were prescribed in daily doses of 50 to 200mg/day because the antihypertensive efficacy of oral diuretics was thought to equate to their natriuretic effects. The rationale for prescribing higher doses of antihypertensive drugs was based on the attempt to have more subjects responding with little attention directed to the occurrence of adverse drug reactions. This practice defined the initial dosing recommendation for thiazide diuretics and resulted in large doses of hydrochlorothiazide, bendroflumethaizide and chlorthalidone being used commonly. It took two decades to realise that the dose-response curve for natriuresis versus BP reduction are quite different. 65

1.3. Narrative review versus systematic review

1.3.1. Introduction

Research evidence can be reviewed using informal or systematic approaches. The informal approach is known as narrative review. In a narrative review, the researcher identifies a subset of trials that could answer the research question and
produces a personal estimate of the parameter of interest based on the impression given by the evidence in the trials, or, alternatively, selects portions of the evidence and reaches conclusions based on them. This approach is subjective in nature and lacks formal tools to extract and summarise research evidence. It is impossible to replicate and therefore is scientifically unsound and can lead to biased conclusions. Narrative reviews are easy and quick to produce, but may delay identification of effective or harmful interventions.\textsuperscript{64}

A systematic review is a scientific process in which the same rules that are applied in the primary studies are applied to the reviewing process; strategies to minimise bias and to maximise precision are incorporated. The systematic review provides an explicit and detailed description of how it was conducted to allow replication.\textsuperscript{66}

The objectives, methods used to identify primary trials, the criteria for inclusion or exclusion of the primary trials, the methods used to assess their methodological quality and summary of results on which conclusions are based are clearly described by the reviewer. This process usually requires much more time and resources to prepare than a narrative review. A systematic review is a “scientific tool which can be used to summarise, appraise, and communicate the results and implications of otherwise unmanageable quantities of research”.\textsuperscript{65} Systematic reviews overcome the limitations of a narrative review.

\textit{1.3.2. Advantages of a systematic review}

A systematic review has many advantages.\textsuperscript{64} It efficiently integrates existing information and provides data for rational decision making. It determines the areas of strength and weaknesses in clinical trials. It is a systematic approach to minimising
biases and random errors. It establishes whether the scientific findings are consistent and can be generalised. It increases the power to detect a difference due to treatment by combining data from individual trials. It can use data from primary trials originally done, to answer a different research question, provided it meets the inclusion criteria and gives information about the subgroup of patients the systematic review is addressing. It identifies implications for future research and clinical practice.

1.3.3. Disadvantages of a systematic review

A systematic review has some disadvantages. It has problems associated with a retrospective data analysis. The process is conducted after the original data were produced and because of this, there is a risk of selection and observer bias although this can be reduced by at least 2 observers determining the eligibility and quality of the primary trials under blinded conditions.

Biases are inherent in the literature such as publication bias, language bias, country of origin bias, etc. Publication bias occurs as a result of the tendency of the investigators to submit, and of reviewers and editors to accept, manuscripts for publication that have positive findings. Publication bias can be reduced by including all relevant primary trials both published and unpublished. Only using published trials has the risk of overestimating the effect of the intervention under evaluation.

1.3.4. Conclusion about the best way to review research evidence

It is important to weigh the advantages and disadvantages of both the narrative review as well as the systematic review. A systematic review is a rigorous scientific process which minimises bias, and can be replicated. Despite its disadvantages, it is still the most effective way to synthesise research evidence. By identifying and combining the results of all research studies already done (to present) and adding
results of those studies that will be completed in the future, this systematic process helps provide an up-to-date answer to the question asked.

1.3.5. The Cochrane Collaboration

The Cochrane Collaboration (CC) is a world-wide collaboration named after Archie Cochrane. The purpose of the CC is to prepare, maintain and disseminate, up-to-date reviews of randomised controlled trials in all areas of health care, and when they are not available, reviews of the most reliable evidence from other sources.

This systematic review has been done using the framework of the Cochrane Collaboration, and it is planned to publish it in the Cochrane library. The most important advantage of using the Cochrane Collaboration RevMan 4.0 in doing this systematic review is that it has the feature of incorporating missed trials or any new trials in future analyses. Also, the feedback from readers world-wide is an ongoing process which can improve the accuracy and completeness of the information.

1.4. Meta-analysis

A systematic review may or may not conduct a meta-analysis. When results of several independent primary studies included in the systematic review are combined statistically into a single estimate of the effect of the intervention, the systematic review is called a meta-analysis. The rationale for meta-analysis, given by Mulrow, is "to increase the power and precision of estimates of treatment effects and exposure risks". The objective of doing a meta-analysis is to increase statistical power, to improve the estimate of the magnitude of a treatment effect, and to make the conclusions more generalizable to a more varied range of patients and treatment protocols. Because it is a retrospective look at the data, the process of combining trials must be rigorous and as well-defined as possible.
1.4.1. Advantages of a meta-analysis

Meta-analysis is used to increase the precision of the conclusions of a systematic review. It can help resolve controversies between conflicting primary trials. It can help clinicians and patients make better decisions. It can guide clinical research by generating hypotheses, or by identifying areas in which insufficient research has been performed or in which additional research may not be necessary. It can also help identify the beneficial or harmful therapies many years before this is achieved by qualitative reviews.

1.4.2. Disadvantages of a meta-analysis

Meta-analysis techniques take into account the different sizes of the individual trials but do not adequately allow for differences or deficiencies in trial design, or differences in objectives. Accepting the results of a group of disparate trials as if they came from a single trial needs careful interpretation. It may not be valid to combine data when differences between the treatment effect of the primary studies are greater than what could be expected by chance alone. This can also be detected by testing for heterogeneity. When the test for heterogeneity is positive, the results must be interpreted with caution.

2. PROTOCOL

This protocol was finalised and on record in January 1999 to explain the rigorous scientific process that would be followed.

2.1. Objectives

Thiazide and ‘thiazide class’ diuretics have proven effectiveness in the treatment of hypertension. However, their BP lowering dose-response effect is not known. This systematic review is the first step to determine the dose-related BP lowering efficacy,
based on all available literature using thiazide and loop diuretics in the treatment of primary hypertension.

**Primary objective:**

To determine the dose-related decrease in systolic and/or diastolic blood pressure due to the thiazide and loop diuretics as compared to a placebo control in the treatment of patients with primary hypertension.

**Secondary objectives:**

To determine the dose-related adverse drug effects leading to patient withdrawal and document the dose-related adverse drug effects of thiazide and loop diuretics on blood levels of potassium, uric acid, creatinine, glucose and the lipid profile.

2.2. **Methodology**

2.2.1. **Data collection and analyses**

Trial inclusion and data abstraction will be done by two independent reviewers. The titles and the abstracts resulting from the search strategies will be independently screened by two reviewers. An article will only be rejected on an initial screen if it is determined from the title or the abstract that the article is not a report of a randomised placebo-controlled trial or did not meet the inclusion criteria. Each trial will be considered as a unit in the systematic review analysis. For each trial, the patients allocated to the placebo control group or the diuretic therapy group will be compared to each other only within that trial and not with patients in any other trial.

Tests for heterogeneity of treatment effect between the trials will be made using a standard chi-square statistic for heterogeneity. Data for blood pressure reduction and blood levels of potassium, uric acid, creatinine, glucose and lipid profile will be
combined using a weighted mean difference method. The weighting factor for each study is the inverse of the within-study variance plus a between-study variance component. Thus, all pooled estimates are DerSimonian-Laird type random effects estimators. Relative risk ratio (RR), risk difference (RD), absolute risk reduction (ARR) = risk difference x 100 and the number needed to treat (NNT) NNT = 1/(risk difference) will also be calculated. The data abstraction form includes details of patient characteristics.

Robustness of the results will be tested using several sensitivity analyses based on quality of the trials, sample size, type of analysis, fixed effect as well as random effect model, trials with isolated systolic hypertension versus other trials, trials sponsored by the pharmaceutical companies versus academic institutions.

Subgroup analysis with respect to age, gender, race, co-morbid factors and the baseline severity of the disease will be calculated. The magnitude of change of treatment after randomisation, from the control to the active group or the active to the control group will be documented if possible.

2.2.2. Quality assessment of each trial

Why assess the quality of studies?

Different studies may examine the same issue in different ways, or indeed examine different, but related issues. The quality and strength of evidence different studies provide to answer a particular research question is likely to vary widely. Therefore, examining the external and internal validity of the study is important to reach valid conclusions.
Quality is a complex concept that is not easy to define or measure. There are a number of tools available to assess the quality of trials but there is little empirical evidence to guide the selection of tools and incorporation of assessments into reviews and decisions. Trials inadequately randomised or double blinded, inadequate or unclear in concealment or allocation, or inappropriately using cross-over design can produce larger treatment effects than similar trials of good quality.\textsuperscript{69} Reports of trials sponsored by pharmaceutical companies overestimate the treatment effect as compared to trials not sponsored by them.\textsuperscript{69}

2.2.2.1. Quality assessed according to the Cochrane Collaboration

RevMan criteria

Based on randomisation and allocation concealment method

A = Clearly adequate: (Centralised randomisation by telephone, randomisation scheme controlled by pharmacy, numbered or coded identical containers administered sequentially, on-site computer system which can only be accessed after entering the characteristics of an enrolled participant, sequentially numbered, sealed, opaque envelopes)

B = Unclear: (Sealed envelopes but not sequentially numbered or opaque, list of random numbers read by someone entering patient into trial (open list), a trial in which the description suggests adequate concealment but other features are suspicious - for example, markedly unequal control and trial groups, stated random, but unable to obtain further details.

C = Clearly inadequate (Alternation, date of birth, day of week, case record number, any allocation procedure transparent before assignment, such as open list of random numbers)
D = Not assigned

2.2.2.2. The Jadad Scale of quality of trials (0-5 score)

The Jadad scale is quick and easy to use. It provides consistent measurements and has construct validity. This scale has been tested and used to identify systematic differences among trials in areas of infertility, homeopathy, anaesthesia, pain relief and neonatology.

One point each is given if randomisation, blinding and description of withdrawals and drop outs are mentioned in the trial. (Total = 3). One additional point each if randomisation/blinding are appropriate and are described in detail or one point each is deducted if randomisation/blinding is inappropriate. (Total = 2)

- If the study was described as randomised: Yes = 1, No = 0
- If the study was described as double blind: Yes = 1, No = 0
- If there was a description of withdrawals in the study: Yes = 1, No = 0
- If randomisation was appropriate: Yes = 1, No = -1
- If blinding was appropriate: Yes = 1, No = -1

Quality is considered as poor if the total score is 2 or less and is considered good if total score is 3 or more. It has been shown that studies that obtain 2 or less points are likely to produce treatment effects which are 35% larger than those produced by trials with 3 or more points. 69

Evidence provided by all trials, regardless of their quality, will be synthesised. Low quality trials versus high quality trials will be compared with the results of the synthesis of the evidence from all trials. If results using both methods are similar then the effect of intervention can be considered to be robust and we have more confidence in the
conclusion. If the results are different, we need to be cautious about the conclusion we draw from the available evidence.

2.2.3. Fixed effect Model

Peto modified the Mantel-Haenszel method and it is also known as the Peto method.\textsuperscript{70} It assumes the underlying treatment effect in each trial is the same and the observed difference is due to chance. This method allows calculation of an estimate known as the pooled odds ratio with its 95\% confidence interval (CI), which could be used not only to test the null hypothesis (that the two interventions, case and control, have equivalent effects) but also to estimate how large, and therefore how relevant, any differential effects are likely to be.

This method weighs by the inverse of the within-study variance. Therefore, the sample size is the factor which determines the importance of individual studies. The authors of this approach also suggest a statistical test for homogeneity of the odds ratio. Such a statistic is assumed to have an approximate chi-square distribution with a degree of freedom one less than the total number of non-zero variances (this is usually exactly equal to the number of studies). It calculates the odds of an event occurring in the treatment group compared with the same odds in the control group. This is not easily interpretable in the clinical setting. Risk difference and NNT have been proposed as the first choice among the fixed-effect methods for the combination of studies with dichotomous data. This method produces inferences which are valid mainly in relation to the set of trials that have been assembled and not to the population of studies asking the same question.\textsuperscript{71}
2.2.4. Random effects model

The Dersimonian and Laird-modified Cochrane method is also called the Dersimonian and Laird method or random effects model. In this model, it is assumed that the treatment effects in different trials are randomly placed around some central value.\textsuperscript{72} This method includes the calculation of the difference between event rates in the treatment and control groups weighted by the inverse of a combination of within-study and between-study variation.\textsuperscript{73} The advantage of using this approach allows determination of whether or not the set of trials being combined are measuring a homogenous effect and, also, permits the estimation of the treatment effect in a hypothetical population of trials addressing the same question compared to a fixed-effect approach. The CI calculated with the random-effects method would be wider if heterogeneity is present, allowing for what has been called "an appropriate degree of statistical caution". The main drawback of this method is that it relies on a single variance to reflect heterogeneity between studies and this makes the results strongly dependent on the number of small trials included in the analysis. If there are many small studies, they may receive disproportionately high weights in the analysis.\textsuperscript{73}

2.3. Search strategy and identification of studies

Electronic databases such as Medline (Jan.1966-June 1999), EMBASE, CINAHL, the Cochrane clinical trial register, Biomedical literature search, the WHO-ISH Collaboration register and bibliographic citations will be used to identify randomised placebo-controlled trials using thiazide or loop diuretics as first-line therapy in the treatment of hypertension. In case of incomplete reports, Medline will be used to search for connected papers to retrieve missing information. Experts in the field will be contacted to get information about ongoing studies or trials about to be published.
The following search strategy was designed to identify pharmacological treatment of hypertension. (A "/" at the end of a term indicates that it is a Medical Subject Heading (MeSH) term; "exp" indicates that the term is exploded (meaning that all MeSH terms nested under the exploded MeSH term are included in the search); "tw" indicates that the term is a text word (meaning the title, abstract and MeSH terms are searched); hypertension/dt returns references coded as Drug Treatment for hypertension; "pt" indicates a publication type; "ti.ab" indicates a search for the text word in the title and abstract but not the MeSH terms; the symbols "$" and "?" are wildcard characters used to search for multiple forms of a word; the search modifier "adj" plus a number between any two terms returns records which contain the two terms within the specified number of words of each other.

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 single-blind method/
7 or/1-6 (all RCT)
8 animal/ not human/
9 7 not 8
10 clinical trial.pt.
11 exp clinical trials/
12 (clin$ adj25 trial$).ti,ab.
13 ((singl$ or doubl$ or treb$) adj25 (blind$ or mask$)).ti,ab.
14 placebos/
15 placebo$.ti,ab.
16 random$.ti,ab.
17 research design/
18 or/10-17
19 18 not 8
20 19 not 9
21 comparative study/
22 exp evaluation studies/
23 follow up studies/
24 prospective studies/
25 (control$ or prospectiv$ or volunteer$).ti,ab.
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28
30 exp antihypertensive agents/
31 exp diuretics/
32 exp Thiazide diuretics/
33.exp loop diuretics/
34 exp furosemide/
35 exp bumetanide/
36 exp ethacrynic acid/
37 exp muzolimine/
38 exp torasemide/
39 exp pirenatnide/
40 exp azosemide/
41 exp ticrynafen/
42 exp tripamide/
43 exp phenoxybenzoic acid/
44 exp indacrinone/
45. exp etozolin/
46 exp ozolinone/
47 exp cicletanine/
48 exp tienilic acid/
49. exp tizolemide/
50 exp hydrochlorothiazide/
51. exp chlorothiazide/
52 exp buthiazide/
53 exp bendroflumethiazide/
54 exp hydroflumethiazide/
55 exp trichloromethiazide
56 exp methylclothiazide/
57 exp polythiazide/
58 exp cyclothiazide/
59 exp cyclopenthiazide
60 exp benzothiadiazines/
61 exp chlorthalidone/
62 exp metolazone/
63 exp quinthazone/
64 exp fenquizone/
65 exp clorexlolone/
66 exp clopamide/
67 exp indapamide/
68 exp diapamide/
69 exp isodiapamide/
70 exp mefruside/
71 exp xipamide/
72 exp xipamide/
73 exp spironolactone/
74 exp amiloride/
75 exp triamterene/
76 or/30-75
77 exp hypertension/
78 exp blood pressure/
79 or/77-78
80 76 and 79
81 80 and 29
2.4. Selection criteria

2.4.1. Types of studies

2.4.1.1. Why are only randomised placebo controlled trials included?

A randomised controlled trial (RCT) is the most reliable way to estimate the effect of an intervention. If done properly, it eliminates selection bias by removing any influence of the investigators on the allocation of the interventions and reduces the risk of serious imbalance in known and unknown important prognostic factors which could influence the course of the process under evaluation. However, selection bias can still be introduced in an RCT, if sequence of treatment allocation is known and if statistical analysis of the results of the trial is not based on all randomised patients (intention-to-treat analysis).

2.4.1.2. Why is blinding to treatment allocation important?

Observer bias could be introduced by the outcome assessor if the treatment allocation is known. Using a double blind treatment allocation reduces this bias.

Despite reducing selection and observer bias a certain amount of variation in the estimates produced by the trial should be expected to be due to random variation or random error, the cause of which is unknown or unlikely to be explained. The precision of estimates of the parameters and their differences from an RCT become more accurate as the sample size increases.

2.4.1.3. Why is a wash-out period with placebo important?

A wash-out period helps to eliminate the carry-over effect of any previous drug therapy and gives an accurate estimate of the baseline blood pressure of the patient
before entry into the study. In trials with a cross-over design, a wash-out period between two drug treatment is therefore necessary for the same reason.

2.4.1.4. Why is a parallel placebo arm required?

The main objective of this systematic review is to determine the dose-dependent blood pressure lowering efficacy of thiazide or loop diuretics compared to a placebo. A placebo arm is required to quantify the effect size due to the placebo effect of the drug. The difference between the size of the total effect in the active treatment group minus the placebo effect will determine the effect due to the pharmacological action of the drug.

Control in an RCT is a set of factors that isolate the experimental effect, minimising, or hopefully, eliminating the possibility that any other factor might explain the outcome of the trial.

2.4.1.5. Why is a baseline measurement important?

This is a built-in protection so that the difference in outcome, between the experimental and control groups at the end of the experiment, is not due to the difference that existed before the experiment was performed.

2.4.1.6. Why is the 3-12 week window selected?

It takes a minimum of 3 weeks for the effect of therapy to be observed. Because hypertension treatment often involves dose titration and addition of other drugs from different classes to achieve the goal BP, the 12 weeks window is a practical upper limit as only data on monotherapy are included. Keeping the trial duration short also helps to include the maximum number of patients, as longer trials have an increased drop-out
rate. Trials more than 12 weeks in duration will be included if they meet the inclusion
criteria and provide data during the 3-12 weeks window using diuretic monotherapy.

2.4.2. Types of participants

2.4.2.1. Based on level of blood pressure

Patients with hypertension are defined as those with systolic blood pressure
(SBP) > 159mm of Hg and/or diastolic blood pressure (DBP) > 89 mm of Hg. Participants will not be restricted by age, gender, baseline risk or any other co-morbid conditions. However, baseline characteristics of the patients and any other co-morbid conditions should be documented to ensure proper randomisation.

2.4.2.2. Based on renal function

Trials with patients who have significant renal insufficiency and a documented serum creatinine level $\geq$ 1.5 times the normal values will be excluded from analysis. Glomerular and tubular function play an important role in determining the response of the kidney to diuretic administration. Renal hemodynamics affect the natriuretic and diuretic action of these agents - the level of sodium excretion is, of course, a function of the amount of sodium filtered. Filtered sodium load is dependent on the glomerular filtration rate (GFR). Therefore, a decrease in GFR decreases the amount of sodium reaching the nephron where diuretics act. Reduced renal function therefore compromises the ability of the diuretic to act and may lead to diuretic resistance and/or the need to increase the dose. Some diuretics (thiazides and carbonic anhydrase inhibitors) tend to reduce GFR as part of their action.

Higher doses of diuretics are required in hypertensive patients with chronic renal failure than in hypertensive patients with normal renal function. Thiazides generally
lose their efficacy with a decline in GFR and larger doses than usual are probably required in such cases. Loop diuretics show a sluggish response if the baseline GFR is low. High levels of organic acids in renal failure compete with diuretics for tubular secretion.

Because the dose response effect is being studied and higher doses of diuretics are required in patients with renal failure, such patients need to be excluded to avoid bias in estimating the effect size.

2.4.3. Types of intervention

Trials of 3 weeks to 12 weeks in duration, comparing single dose of a thiazide or loop diuretic, as monotherapy versus a placebo control in the treatment of primary hypertension will be included. If all the patients in the trial are given a titrated dose regardless of their blood pressure levels, the higher dose given for the specified duration of time can be included. Stepped-up therapy given only to non-responders would produce bias in the results and will not be included in the analysis. Potassium supplementation will be allowed in patients with low serum potassium levels. In cross-over trials with no wash-out period between two treatment periods, only data of the first phase of active treatment versus a parallel placebo group will be included.

Drugs within thiazide diuretic class include:

- hydrochlorothiazide
- bendroflumethiazide
- methylclothiazide
- cyclopenthiazide
- quinethazone

- chlorothiazide
- hydroflumethiazide
- polythiazide
- chlorthalidone
- fenquizone

- buthiazide
- trichloromethiazide
- cyclothiazide
- metolazone
- clorexolone
Drugs within loop diuretic class include:

- furosemide
- bumetanide
- piretanide
- torasemide
- azosemide
- ethacrynic acid
- ticrynafen
- tripamide
- phenoxybenzoic acid
- muzolimine, indacrinone
- etozolin
- ozolinone
- cicletanine
tienilic acid
- tizolemide.

2.4.4. Types of outcome measures

The outcome measures that will be used for data abstraction will be:

1. The trough and/or peak systolic and diastolic blood pressure (sitting, standing or supine) at baseline following the washout period. (Peak level is defined as BP measurement within 12 hours of the dose and trough level is defined as BP levels between 12 and 24 hours of the dose).

2. The trough and/or peak systolic and diastolic blood pressure at the 3 and 12 weeks of treatment.

3. The standard deviations (SD) of changes in the systolic and diastolic BP values are included.

4. If more than one blood pressure measurement is available, the mean weighted change of SBP and DBP from the baseline with SD of the difference in the 3-12 weeks treatment period will be used.

5. The number of patient withdrawals due to dose-related adverse events during the specified period of time the patient is taking the drug.
6. The baseline and during treatment (3 to 12 weeks) levels of serum potassium, uric acid, creatinine, glucose and lipid profile with SD of the change. If more than one measurement is available, the weighted average levels will be calculated.

2.4.5. Exclusion criteria

The following will be excluded:

Non-randomised trials; trials of duration less than 3 weeks, trials in which the dose of the medication is titrated only in non-responders to achieve the defined goal DBP, trials using drug therapy combinations including a thiazide or loop diuretic with other classes of drugs as first line treatment, or using other classes of drugs with thiazide or loop diuretics as first line therapy; trials reporting placebo blood pressure levels following wash-out period and comparing them with the treatment levels following randomisation; trials including patients with significant renal insufficiency (creatinine levels ≥ 1.5 times the normal value).

Every attempt will be made to extract information from figures or bibliographic references. Trials which are published many times using the same group of patients will be counted only once. Trials that meet the inclusion criteria but do not give the data required for analysis will be included if the data can be obtained from the authors.

2.5. Problems encountered during data search and abstraction

2.5.1. Problems during data search

Since the indexing of trials in the electronic database were found to be inaccurate and incomplete, the search strategy was designed to be all-inclusive. Most of the trials in hypertension have a placebo wash-out period prior to random allocation of treatment. The database does not index parallel placebo controlled trials separately; therefore, most trials had to be carefully screened to distinguish for appropriate design.
All trials using stepped-up therapy were screened to look for data on monotherapy given for at least a 3 week duration.

Trials using combination therapy could not be excluded using a search strategy because such trials could have a parallel monotherapy and placebo arm. Trials with insufficient information in the abstract to make a decision were termed probable and retrieved. The full text of these reports was read prior to including or excluding them. Because the study design details were missing in the abstract of many trials, these trials were also retrieved. Many trials that seemed to meet the inclusion criteria on reading the abstract had to be excluded on detailed analyses and the reasons for exclusion are documented in the 'characteristics of excluded studies'.

2.5.2. Problems during data abstraction

Many problems were encountered and the following are a few of them:

Different trial designs with incomplete information about the details of the design; different ways in which data were reported; lack of uniformity in reporting blood pressure levels; presenting BP data as two dimensional or sometimes three dimensional figures using different scales made data abstraction difficult or impossible. The standard deviation of the change in blood pressure is often omitted. Some trials meeting inclusion criteria had to be excluded due to non-reporting of the baseline blood pressure. Most randomised trials did not report baseline metabolic parameters and reported values only at the end of treatment. When useful important data are not reported in the published trial, the best available evidence is not possible to compile. Improper reports of trials lead to an enormous waste of resources and time.
2.6. Data conversion and imputing standard deviation (SD) of change

2.6.1. Imputing SD of change for BP data

8 of the 36 trials meeting the inclusion criteria gave information on the SD of change in SBP and DBP. For all other trials, the mean weighted SD of change was calculated based on information in these trials. The mean weighted SD of change was 11.6 mm Hg for SBP and 7.5 mm Hg for DBP in the control group and 13.1 mm Hg for SBP and 8.4 mm Hg for DBP in the treatment group.

2.6.2. Data conversion and imputing SD of change for metabolic data

Serum potassium, glucose, uric acid, triglyceride, cholesterol levels were converted to mmol/L and serum creatinine levels were converted to μmol/L in all trials. The following conversion factor were used. For serum potassium mEq/L was equal to mmol/L; serum glucose 0.0555mg/dL = mmol/L; serum uric acid 0.0595mg/dL = mmol/L; serum triglycerides 0.01128mg/dL = mmol/L; serum total cholesterol 0.02586 mg/dL = mmol/L and serum creatinine 0.0884 mg/dL times 1000 = μmol/L.

16 trials gave data on metabolic adverse events. In 7 trials out of the 16, SD of change was given or could be calculated. The SD of change for metabolic parameters when not given was imputed from the SHEP trial\textsuperscript{45} evaluating 2218 patients in the treatment group and 2202 patients in the control group. The SD values of change imputed from this trial in the treatment and placebo groups, respectively, were 0.5mmol/ L and 0.4 mmol/ L for serum potassium ; 0.1 mmol/ L and 0.08 mmol/ L for serum uric acid; 2.4 mmol/ L and 2.0 mmol/ L for serum glucose and 1.2 mmol/ L and 1.1 mmol/ L for serum cholesterol. Because SD of change for serum triglycerides and creatinine was not available in the SHEP trial, the TOMHS\textsuperscript{74} study that evaluated 136 patients was used. The SD values of change in the treatment and placebo groups, respectively, were 0.06
mmol/L and 0.03 mmol/L for serum triglycerides and 0.9 μmol/L and 0.4 μmol/L for serum creatinine.
3. RESULTS

3.1. Search findings

Table 2: Search findings using the detailed search strategy

<table>
<thead>
<tr>
<th>Criteria of search</th>
<th>Total number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials identified by the search strategy</td>
<td>2156</td>
</tr>
<tr>
<td>Trials excluded on reading titles and abstracts</td>
<td>1688</td>
</tr>
<tr>
<td>Trials retrieved for detailed reading</td>
<td>468</td>
</tr>
<tr>
<td>Trials excluded after detailed reading</td>
<td>393</td>
</tr>
<tr>
<td>Number of trials meeting inclusion criteria</td>
<td>75</td>
</tr>
<tr>
<td>Of the 75 trials meeting the inclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Data available</td>
<td>36</td>
</tr>
<tr>
<td>Data not available</td>
<td>39</td>
</tr>
<tr>
<td>Characteristics of included studies</td>
<td>36</td>
</tr>
<tr>
<td>Characteristics of excluded studies</td>
<td>39</td>
</tr>
</tbody>
</table>
### 3.2. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Description of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosini et al 1998(^75)</td>
<td><strong>Design:</strong> MCRDBPC dose finding study with a washout period of 1 month and study duration of 2 months.</td>
</tr>
<tr>
<td></td>
<td><strong>Country:</strong> Europe</td>
</tr>
<tr>
<td></td>
<td><strong>Quality:</strong> Cochrane method = B; Jadad score = 1</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> DBP 95-114mm Hg for inclusion into the trial. Mean age of patients was 54 years. Male 51.5%. Baseline BP was 164.5/101.7 mm Hg in the treatment group and 164.4/102.5 in the control group. Baseline pulse pressure was 62.8 in the treatment group and 61.9 in the control group.</td>
</tr>
<tr>
<td></td>
<td><strong>Interventions:</strong> Indapamide SR 1.5 mg/day, 2.0 mg/day, 2.5 mg/day or indapamide 2.5 mg/day or placebo.</td>
</tr>
<tr>
<td></td>
<td><strong>Primary and secondary outcomes:</strong> Change from baseline in supine DBP, supine SBP, standing DBP and SBP.</td>
</tr>
<tr>
<td></td>
<td><strong>Notes:</strong> No placebo arm data for metabolic data. Indapamide 2.5 SR and 2.5 IR results are added and presented as weighted mean changes in SBP, DBP and WDAE.</td>
</tr>
<tr>
<td>Mallion et al is a duplicate publication of the same trial.</td>
<td></td>
</tr>
<tr>
<td>Benz et al 1998(^76)</td>
<td><strong>Design:</strong> RDBPC trial with a washout period of 2-4 weeks and study duration of 8 weeks.</td>
</tr>
<tr>
<td></td>
<td><strong>Country:</strong> USA</td>
</tr>
<tr>
<td></td>
<td><strong>Quality:</strong> Cochrane method = B; Jadad score = 3</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> DBP 95-115 mm Hg for inclusion into the trial. Mean age of patients was 52 years. Male 57%. Baseline BP was 152.8/101.5 mm Hg in the treatment group and 152.7/101.4</td>
</tr>
</tbody>
</table>
in the control group. Baseline pulse pressure was 51.3 in both the treatment and the control group.

**Interventions:** HCTZ 12.5 mg/day, or HCTZ 25 mg/day or placebo.

**Primary and secondary outcomes:** Mean change in the trough SBP and DBP from baseline between treatment and placebo group

**Notes:** SD of change in BP not given. WDAE not given for each treatment group.

| Bradley et al 1993<sup>77</sup> | **Design:** RDBPC trial with a washout period of 8 weeks and study duration of 12 weeks.  
**Country:** USA  
**Quality:** Cochrane method = B; Jadad score = 3  
**Participants:** Non-smoking men with DBP 90-104 mm Hg for inclusion into the trial. Mean age of patients was 51 years. Male 100%. Baseline BP was 140/92 mm Hg in the treatment group and 140/91 in the control group. Baseline pulse pressure was 48 in the treatment group and 54 in the control group.  
**Interventions:** Chlorthalidone 45 mg/day or placebo.  
**Primary and secondary outcomes:** Change from baseline in LDL-3, LDL-1, LDL-2, TG, TC, VLDL, HDL-C, HDL-2, HDL-3, glucose, insulin, SBP and DBP, and WDAE.  
**Notes:** No SD for BP data. WDAE none. |
| --- | --- |
| Capone et al 1983<sup>78</sup> | **Design:** RDBPC trial with a washout period of 6 weeks and study duration of 8 weeks.  
**Country:** USA  
**Quality:** Cochrane method = B; Jadad score = 3 |
<table>
<thead>
<tr>
<th>Participants:</th>
<th>DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 52 years. Male 66%. Baseline BP was 152/102.8 mm Hg in the treatment group and 153/103.8 in the control group. Baseline pulse pressure was 49.2 in the treatment group and 49.5 in the control group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions:</td>
<td>Indapamid 1.0 mg/day, 2.5 mg/day, 5.0 mg/day or placebo.</td>
</tr>
<tr>
<td>Primary and secondary outcomes:</td>
<td>Change from baseline in supine SBP and DBP.</td>
</tr>
<tr>
<td>Notes:</td>
<td>BP data from the figure. No SD for metabolic data. Number of subjects unknown for metabolic data. WDAE not given.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carlsen et al 1990\textsuperscript{79}</th>
<th>Design: RDBPC dose ranging study with a washout period of 6 weeks and study duration of 12 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country:</td>
<td>Denmark</td>
</tr>
<tr>
<td>Quality:</td>
<td>Cochrane method = A; Jadad score = 5</td>
</tr>
<tr>
<td>Participants:</td>
<td>DBP 100-120 mm Hg for inclusion into the trial. Mean age of patients was 57.4 years. Male 40%. Baseline BP was 165.2/104 mm Hg in the treatment group and 161.9/101.8 in the control group. Baseline pulse pressure was 61.2 in the treatment group and 60.1 in the control group.</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Bendrofluazide 1.25 mg/day, 2.5 mg/day, 5.0 mg/day 10.0 mg/day or placebo.</td>
</tr>
<tr>
<td>Primary and secondary outcomes:</td>
<td>Change from baseline in sitting SBP, DBP and metabolic data.</td>
</tr>
<tr>
<td>Notes:</td>
<td>Mean ± SEM given for BP data at 4 and 10-12 weeks, for metabolic data. WDAE were = 9 (2 in the placebo, 1.25 mg, 2.5 mg and 10.0 mg group and 1 in the 5 mg group).</td>
</tr>
<tr>
<td>Study</td>
<td>Design: MCRDBPC trial with a washout period of 4 weeks and study duration of 12 weeks.</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Country: USA</td>
</tr>
<tr>
<td></td>
<td>Quality: Cochrane method = B; Jadad score = 0</td>
</tr>
<tr>
<td></td>
<td>Participants: DBP 100-114 mm Hg for inclusion into the trial. Mean age of patients was 53.5 years. Male 58.2%. Baseline BP was 155/103 mm Hg in both the treatment and in the control group. Baseline pulse pressure was 52 in both the treatment and in the control group.</td>
</tr>
<tr>
<td></td>
<td>Interventions: HCTZ 12.5 mg/day, HCTZ 25.0 mg/day or placebo.</td>
</tr>
<tr>
<td></td>
<td>Primary and secondary outcomes: Change from baseline in trough mean sitting SBP and DBP.</td>
</tr>
<tr>
<td></td>
<td>Notes: BP data were obtained from the figure. Mean change from placebo group with SD of change is mentioned. WDAE data not given.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design: RDBPC trial with a washout period of 4 weeks and study duration of 6 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Country: USA</td>
</tr>
<tr>
<td></td>
<td>Quality: Cochrane method = B; Jadad score = 3</td>
</tr>
<tr>
<td></td>
<td>Participants: DBP 90-114 mm Hg for inclusion into the trial. Mean age of patients not given, range was 30-71 years. Male 43%. Baseline BP was 150.1/97.1 mm Hg in the treatment group and 150.9/99.0 in the control group. Baseline pulse pressure was 53 in the treatment group and 51 in the control group.</td>
</tr>
<tr>
<td></td>
<td>Interventions: Metolazone 0.5 mg/day, 1.0 mg/day, 2.0 mg/day or placebo.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dean et al 1971</td>
<td>RDBPC dose finding study with washout period not reported in the study</td>
</tr>
<tr>
<td>Fernandez et al</td>
<td>RDBPC cross-over trial with a washout period of 3 weeks and study duration of 10 weeks. Each treatment period of 4 weeks with 2 week washout between treatment.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Fernandez et al 1994⁸⁴</td>
<td>RDBPC trial with a washout period of 4 weeks and study duration of 2 months.</td>
</tr>
<tr>
<td>Ferrara et al 1984⁸⁵</td>
<td>RDBPC trial with a washout period of 2 weeks and study duration of 2 months.</td>
</tr>
<tr>
<td>Study</td>
<td>Design: RDBPC trial with a washout period of 2 weeks and study duration of 2 months.</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fiddes et al 1997\textsuperscript{86}</td>
<td><strong>Interventions:</strong> Chlorthalidone 25 mg/day or placebo. <strong>Primary and secondary outcomes:</strong> SBP and DBP. WDAE data not given. <strong>Notes:</strong> SD of change for BP data not given. Metabolic data not given.</td>
</tr>
<tr>
<td></td>
<td><strong>Participants:</strong> DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 69.7 years. Male 55%. Baseline BP was 159.3/98.8 mm Hg in the treatment group and 160.3/99.8 in the control group. Baseline pulse pressure was 60.5 in both the treatment group and in the control group. <strong>Interventions:</strong> Indapamide 1.25 mg/day or placebo. <strong>Primary and secondary outcomes:</strong> Change from baseline in supine DBP, SBP. Metabolic data are given. <strong>Notes:</strong> For BP and metabolic data the number of subjects change over duration of the treatment period.</td>
</tr>
</tbody>
</table>
| Hall et al 1994\textsuperscript{87} | **Design:** RDBPC trial with a washout period of 4 weeks and study duration of 8 weeks. **Country:** USA **Quality:** Cochrane method = B; Jadad score = 3 **Participants:** DBP 95-110 mm Hg for inclusion into the trial. Mean age of patients was 50.2 years. Male 40%. Baseline BP was 150.2/100.1 mm Hg in the treatment group and 149.8/99.6 in
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Quality</th>
<th>Participants</th>
<th>Interventions</th>
<th>Primary and secondary outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jounela et al 1994</td>
<td>RDBPC dose ranging trial with a washout period of 4 weeks and study duration of 6 weeks.</td>
<td>Scandinavia</td>
<td>Cochrane method = A; Jadad score = 5</td>
<td>DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 48.5 years. Male 39.6%. Baseline BP was 152.8/99.3 mm Hg in the treatment group and 152.5/99.8 mm Hg in the control group. Baseline pulse pressure was 53.5 in the treatment group and 52.7 in the control group.</td>
<td>HCTZ 3 mg/day, 6 mg/day, 12.5 mg/day, 25 mg/day or placebo.</td>
<td>Change from baseline in mean standing DBP and SBP. Metabolic data given.</td>
<td>Supine BP change from baseline given with SD of change.</td>
</tr>
<tr>
<td>Kayanakis et al 1987</td>
<td>MCRDBPC dose finding study with a washout period of 2 weeks and study duration of 8 weeks.</td>
<td>France</td>
<td>Cochrane method = B; Jadad score = 1</td>
<td>SBP 160-200 mm Hg and DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 53.5 years.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Quality</td>
<td>Participants</td>
<td>Interventions</td>
<td>Primary and secondary outcomes</td>
<td>Notes</td>
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</tr>
<tr>
<td>Krantz et al 1988</td>
<td>RDBPC trial with a washout period of 1 month and 6 weeks</td>
<td>Canada</td>
<td>B; Jadad score = 3</td>
<td>DBP 90-108 mm Hg for inclusion into the trial. Mean age of patients was 45.2 years. Male 100%. Baseline BP was 138/89 mm Hg in the treatment group and 135/87 mm Hg in the control group. Baseline pulse pressure was 49.5 in the treatment group and 49.2 in the control group.</td>
<td>HCTZ 25 mg/day b.i.d. for 2 weeks followed by HCTZ 50 mg/day b.i.d. or placebo for 4 weeks in all patients.</td>
<td>SBP and DBP.</td>
<td>SD for BP data are not given.</td>
</tr>
<tr>
<td>Lacourciere et al 1994</td>
<td>RDBPC trial with a washout period of 4 weeks and study duration of 12 weeks.</td>
<td>Canada</td>
<td>B; Jadad score = 3</td>
<td>DBP 95-110 mm Hg for inclusion into the trial.</td>
<td>HCTZ 25 mg/day or placebo.</td>
<td>Change from baseline in trough supine SBP and DBP. Serum potassium levels given.</td>
<td>BP data from the figure without any SD information. No SD information on serum potassium levels. WDAE none.</td>
</tr>
</tbody>
</table>
| **Lawton et al 1979**\(^{92}\) | **Design:** RDBPC cross-over trial with a washout period of 4 weeks and study duration of 1 month. Each treatment phase was 4 weeks in duration.  
**Country:** USA  
**Quality:** Cochrane method = B; Jadad score = 0  
**Participants:** DBP 95-105 mm Hg for inclusion into the trial. Mean age of patients was 37 years. Male 71%. Baseline BP was 135/93 mm Hg in the treatment group and 137/93 in the control group. Baseline pulse pressure was 42 in the treatment group and 44 in the control group.  
**Interventions:** Chlorthalidone 50 mg/day or placebo.  
**Primary and secondary outcomes:** Change from baseline in SBP and DBP. WDAE data not given.  
**Notes:** BP data available with SD at end of 1 month. Metabolic data not given. |
| **Lucas et al 1985**\(^{93}\) | **Design:** RDBPC dose finding study with a washout period of 4 weeks and study duration of 4 weeks.  
**Country:** USA |
| Quality: Cochrane method = B; Jadad score = 2 |
| Participants: DBP 100-115 mm Hg for inclusion into the trial. Mean age of patients was 50 years. Male 65%. Baseline SBP not given. Baseline DBP was 103.7 mm Hg. |
| Interventions: HCTZ 50 mg/day, 100 mg/day, or placebo. |
| Primary and secondary outcomes: Mean change from baseline in SBP and DBP. |
| Notes: BP data at 3 and 4 weeks abstracted from the figure with no information about SD. Metabolic data given as percentage and not actual values. WDAE not given. |

| MacKay et al 1996 | Design: RDBPC trial with a washout period of 4 weeks and study duration of 12 weeks. |
| Country: USA |
| Quality: Cochrane method = B; Jadad score = 3 |
| Participants: DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 53.5 years. Male 60%. Baseline BP was 152.2/100.9 mm Hg in the treatment group and 152.3/101.3 in the control group. Baseline pulse pressure was 51.3 in the treatment group and 51 in the control group. |
| Interventions: HCTZ 12.5 mg/day or placebo. |
| Primary and secondary outcomes: Change from baseline in trough mean sitting SBP and DBP. WDAE is given. |
| Notes: No SD for BP data. WDAE none. Metabolic data are not given. |

| Materson et al 1978 | Design: MRDBPC trial with a washout period of 4 weeks and study duration of 12 weeks. |
| Country: USA |
### McVeigh et al 1988\(^6\)

The same trial has 3 more publications.

<table>
<thead>
<tr>
<th>Quality: Cochrane method = A; Jadad score = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants:</strong> DBP 90-110 mm Hg for inclusion into the trial.</td>
</tr>
<tr>
<td>Mean age of patients was 57 years. Male 41.5%. Baseline BP was 166.7/97 mm Hg in the treatment group and 157/94 in the control group. Baseline pulse pressure was 69.7 in the treatment group and 63 in the control group.</td>
</tr>
<tr>
<td><strong>Interventions:</strong> Cyclopenthiazide 50 μg/day, 125 μg/day, 500 μg/day or placebo.</td>
</tr>
<tr>
<td><strong>Primary and secondary outcomes:</strong> Sitting SBP and DBP. WDAE mentioned. Metabolic data on serum levels of TG, TC, HDL-C and LDL-C given.</td>
</tr>
<tr>
<td><strong>Notes:</strong> SD of change of BP data not given. SD of the metabolic data are not given instead 95% confidence limits are given. Discrepancy in the number of patients in the different...</td>
</tr>
</tbody>
</table>
| Morledge et al 1986<sup>97</sup> | **Design:** RDBPC trial with a washout period of 2 weeks and study duration of 12 weeks  
**Country:** USA  
**Quality:** Cochrane method = A; Jadad score = 3  
**Participants:** SBP of 160 mm Hg or more for inclusion into the trial. Mean age of patients was 73 years. Male 38.5%. Baseline BP was 176/84 mm Hg and pulse pressure was 92 in both the treatment group and in the control group.  
**Interventions:** Chlorthalidone 12.5 mg/day, 25 mg/day, 50 mg/day or placebo.  
**Primary and secondary outcomes:** SBP and DBP at week 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12. Serum potassium levels at week 6 and 12. Serum uric acid levels at week 12.  
**Notes:** BP data abstracted from the figure with number of patients and SD information missing. Number of subjects for metabolic data is not given. Patients received potassium supplements at the discretion of the physicians. |
| --- | --- |
| Muiesan et al 1987<sup>98</sup> | **Design:** RDBPC dose finding study with a washout period of 3 weeks and study duration of 4 weeks.  
**Country:** Italy  
**Quality:** Cochrane method = B; Jadad score = 1  
**Participants:** DBP 100-109 mm Hg for inclusion into the trial. Mean age of patients was 49 years. Male 50.6%. Baseline BP was 175/105 mm Hg in the treatment group and 175/104 in the control group. Baseline pulse pressure was 70 in the treatment group and 71 in the control group.  
**Interventions:** HCTZ 25 mg/day or placebo. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Country</th>
<th>Quality</th>
<th>Participants</th>
<th>Interventions</th>
<th>Primary and secondary outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persson et al 1996</td>
<td>MCRDBPC dose finding study with a washout period of 4 weeks and study duration of 8 weeks.</td>
<td>Germany and Sweden</td>
<td>Cochrane method = B; Jadad score = 3</td>
<td>DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 70 years. Male 57%. Baseline BP was 171/102 mm Hg in the treatment group and 172/103 in the control group. Baseline pulse pressure was 69 in both the treatment and in the control group.</td>
<td>HCTZ 25 mg/day or placebo.</td>
<td>Change from baseline in trough mean sitting SBP and DBP. WDAE is given.</td>
<td>BP data for the placebo abstracted from the figure. No SD for the BP data. 3-12 weeks information for metabolic data (serum potassium and uric acid level) is not given.</td>
</tr>
<tr>
<td>Roque et al 1996</td>
<td>RDBPC trial with a washout period of 1 week and study duration of 8 weeks.</td>
<td>Argentina</td>
<td>Cochrane method = B; Jadad score = 3</td>
<td>DBP 95-115 mm Hg for inclusion into the trial. Mean age of patients was 62.5 years. Male 41%. Baseline BP was 160.2/98.8 mm Hg in the treatment group and 163.4/99.1 in the control group. Baseline pulse pressure was 61.4 in the</td>
<td></td>
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</tbody>
</table>
| Schoenberger et al 1995\textsuperscript{101} | Design: RDBPC trial with a washout period of 4 weeks and study duration of 12 weeks.  
Country: USA  
Quality: Cochrane method = B; Jadad score = 3  
Participants: DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 53 years. Male 59%. Baseline BP was 152.2/100.9 mm Hg in the treatment group and 152.3/101.3 in the control group. Baseline pulse pressure was 51.3 in the treatment group and 51 in the control group.  
Interventions: HCTZ 12.5 mg/day or placebo.  
Primary and secondary outcomes: Change from baseline in supine SBP and DBP. WDAE is given.  
Notes: SD of the change in BP data is given. WDAE none. |
| Siegel et al 1994\textsuperscript{102}  
Multiple publications in 1991 and 1992 | Design: RDBPC trial with a washout period of 4 weeks and study duration of 8 weeks.  
Country:  
Quality: Cochrane method = A; Jadad score = 4  
Participants: Patients taking diuretics for 6 months with DBP < 95 mm Hg or patients with history of hypertension taking non-diuretic antihypertensive drugs or had DBP ≥ 90 to < 105 mm Hg for inclusion into the trial. Mean age of patients was 61 years. Male 100%. Baseline BP was 141.5/85.7 mm Hg in the treatment group and 64.3 in the control group.  
Interventions: HCTZ 12.5 mg/day or placebo.  
Primary and secondary outcomes: Change from baseline in supine SBP and DBP. WDAE is given.  
Notes: Metabolic data not given. |
| **Smith et al 1986**<sup>103</sup> | **Design:** MCRDBPC dose finding study with a washout period of 1 month and a study duration of 4 weeks for monotherapy.  
**Country:** USA  
**Quality:** Cochrane method = A; Jadad score = 5  
**Participants:** SBP 160-219 mm Hg and DBP less than 90 mm Hg for inclusion into the trial. Mean age of patients more than 70 years. Male 36%. Baseline BP was 172/75 mm Hg in the treatment group and 174/77 in the control group. Baseline pulse pressure was 97 in both the treatment group and in the control group.  
**Interventions:** Chlorthalidone 25 mg/day or placebo.  
**Primary and secondary outcomes:** SBP, DBP and serum potassium level.  
**Notes:** BP data abstracted from the figure with no information about SD. No information on SD given for serum potassium level. |
| **Taylor et al 1988**<sup>104</sup> | **Design:** RDBPC trial with a washout period of 6 weeks and study duration of 16 weeks.  
**Country:** Johannesburg |
<table>
<thead>
<tr>
<th>Quality: Cochrane method = B; Jadad score = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants:</strong> DBP 95-115 mm Hg for inclusion into the trial. Mean age of patients was 61 years. Male 7.5%. Baseline BP was 157/96 mm Hg in the treatment group and 158/96 in the control group. Baseline pulse pressure was 61 in the treatment group and 62 in the control group.</td>
</tr>
<tr>
<td><strong>Interventions:</strong> Indapamide 2.5 mg/day or placebo.</td>
</tr>
<tr>
<td><strong>Primary and secondary outcomes:</strong> Standing SBP and DBP at week 4, 8, 12 and 16. Metabolic data is given.</td>
</tr>
<tr>
<td><strong>Notes:</strong> Following 8 weeks treatment all patients received magnesium chloride SR 535mg tablets in two doses. Potassium supplement given only to patients with serum potassium levels less than 3.5 mmol/L. No SD information for BP data or metabolic data. WDAE during 3-12 weeks not given.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Design: RDBPC trial with a washout period of 4 weeks and study duration of 4 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country:</strong> Netherland</td>
</tr>
<tr>
<td><strong>Quality:</strong> Cochrane method = B; Jadad score = 1</td>
</tr>
<tr>
<td><strong>Participants:</strong> Baseline characteristics were different. DBP 95-120 mm Hg for inclusion into the trial. Median age of patients was 48 years. Male 73%. Baseline BP was 159/100 mm Hg in the treatment group and 167/107 in the control group. Baseline pulse pressure was 59 in the treatment group and 60 in the control group.</td>
</tr>
<tr>
<td><strong>Interventions:</strong> Furosemide 60 mg/day or placebo.</td>
</tr>
<tr>
<td><strong>Primary and secondary outcomes:</strong> Standing SBP and DBP. WDAE is given.</td>
</tr>
<tr>
<td><strong>Notes:</strong> BP data at 4 weeks with SD is given. Metabolic data are</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td>Vardan et al 1987&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verho et al 1986&lt;sup&gt;107&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Primary and secondary outcomes:</strong> Standing SBP and DBP. WDAE is given.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Notes:</strong> No information about SD for BP data. Metabolic data are not given. WDAE none.</td>
</tr>
<tr>
<td><strong>Weilder et al 1995</strong>&lt;sup&gt;108&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Country:</strong> USA</td>
</tr>
<tr>
<td><strong>Quality:</strong> Cochrane method = B; Jadad score = 1</td>
</tr>
<tr>
<td><strong>Participants:</strong> DBP 95-110 mm Hg for inclusion into the trial. Mean age of patients was 60.9 years. Male 48%. Baseline BP was 150.7/98.9 mm Hg in the treatment group and 152.5/98.7 in the control group. Baseline pulse pressure was 51.8 in the treatment group and 53.8 in the control group.</td>
</tr>
<tr>
<td><strong>Interventions:</strong> Indapamide 1.25 mg/day or placebo.</td>
</tr>
<tr>
<td><strong>Primary and secondary outcomes:</strong> Change from baseline in trough mean sitting SBP and DBP. WDAE is given.</td>
</tr>
<tr>
<td><strong>Notes:</strong> Number of subjects change over duration of the trial for the BP data. Information on SD of BP data not given. Metabolic data are not given.</td>
</tr>
<tr>
<td><strong>Werthiemer et al 1971</strong>&lt;sup&gt;109&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Country:</strong> USA</td>
</tr>
<tr>
<td><strong>Quality:</strong> Cochrane method = B; Jadad score = 3</td>
</tr>
<tr>
<td><strong>Participants:</strong> DBP 90-129 mm Hg for inclusion into the trial. Mean age of patients was 58.5 years. Male 43.5%. Baseline BP in all patients was 177/107 mm Hg and pulse pressure was 70.</td>
</tr>
<tr>
<td><strong>Interventions:</strong> Furosemide 80 mg/day or placebo.</td>
</tr>
</tbody>
</table>
**Primary and secondary outcomes:** SBP and DBP. WDAE and metabolic data are given.

**Notes:** Group I furosemide group can be compared to group II placebo group and is the only valid comparison. WDAE none.

**Wiggam et al 1999**<sup>10</sup>

**Design:** MCRDBPC dose finding study with a washout period of 1 month and study duration of 2 months.

**Country:** Europe

**Quality:** Cochrane method = B; Jadad score = 2

**Participants:** DBP 95-114 mm Hg for inclusion into the trial. Mean age of patients was 54 years. Male 51.5%. Baseline BP was 164.5/101.7 mm Hg in the treatment group and 164.4/102.5 in the control group. Baseline pulse pressure was 62.8 in the treatment group and 61.9 in the control group.

**Interventions:** Indapamide SR 1.5 mg/day, 2.0 mg/day, 2.5 mg/day or indapamide 2.5 mg/day or placebo.

**Primary and secondary outcomes:** Change from baseline in supine DBP.

**Notes:** No placebo arm data for metabolic data. Indapamide 2.5 SR and 2.5 IR results are added and presented as weighted mean changes in SBP, DBP and WDAE.
### 3.3. Characteristics of excluded studies

Table 4: Documentation of the reason why certain studies meeting the inclusion criteria were excluded

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman D et al 1979(^{111})</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1(^{st}) 4 weeks of chlorthalidone 25 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Batterman et al 1966(^{112})</td>
<td>Results of multiple trials.</td>
</tr>
<tr>
<td>Carreta et al 1988(^{113})</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1(^{st}) 3 months of indapamid 2.5 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given. One more publication of the same trial but placebo data are not given.</td>
</tr>
<tr>
<td>Chalmers et al 1982(^{114})</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1(^{st}) 5 weeks of indapamid 2.5 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Chalmers et al 1986(^{115})</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1(^{st}) 4 weeks of HCTZ 50 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Dupont et al 1988(^{116})</td>
<td>RDBPCT comparing torasemide 2.5 mg/day versus placebo for a duration of 12 weeks. The study meets the criteria but baseline BP and metabolic data are not given, so change from</td>
</tr>
</tbody>
</table>
baseline could not be calculated. Change from placebo at the end of 12 weeks therapy given for SBP, DBP and metabolic data. None of the patients withdrew due to adverse events

<table>
<thead>
<tr>
<th>Elliot WJ et al 1991&lt;sup&gt;117&lt;/sup&gt;</th>
<th>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for first 4 weeks of indapamide 2.5 mg/day, HCTZ 25 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall MA et al 1992&lt;sup&gt;118&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria. The dose of HCTZ was doubled in nonresponders. However, data for 1&lt;sup&gt;st&lt;/sup&gt; 4 months of HCTZ 12.5 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Galloway et al 1974&lt;sup&gt;119&lt;/sup&gt;</td>
<td>RDBC cross over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 4 weeks of bendrofluazide 2.5 mg/day or placebo monotherapy is valid to use per protocol requirement and is not given.</td>
</tr>
<tr>
<td>Gleerup et al 1996&lt;sup&gt;120&lt;/sup&gt;</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 4 weeks of HCTZ 24 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Goldman et al 1980&lt;sup&gt;121&lt;/sup&gt;</td>
<td>VA study. A RDBCPC trial. The trial meets the inclusion criteria although baseline DBP inclusion range was 85-105 mm Hg. The mean DBP was &gt; 90 mm Hg. Data for step I of chlorthalidone 50 mg/day versus placebo monotherapy are valid to use per protocol requirement and the 3-12 week data are not given. The step II data cannot be used as the dose of chlorthalidone was doubled only in non-responders. Data at the end of one year are available.</td>
</tr>
<tr>
<td>Grimm RH et al</td>
<td>RDBPC cross-over trial with no washout period between active</td>
</tr>
<tr>
<td>Year</td>
<td>Study Description</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td>1981</td>
<td>Treatment. The trial meets the inclusion criteria but data for 1st 6 weeks of HCTZ 100 mg/day, chlorthalidone 100 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Grimm et al 1996</td>
<td>TOMHS study. Results are given as active treatment group and not as monotherapy to individual active drug treatment.</td>
</tr>
<tr>
<td>Homuth et al 1993</td>
<td>This trial meets the inclusion criteria but data from the figure cannot be abstracted or interpreted.</td>
</tr>
<tr>
<td>Horvath J et al 1979</td>
<td>RDBC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 8 months of bendrofluazide 5 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given. Also, BP data are recorded as mean arterial pressure and SBP and DBP values are not given.</td>
</tr>
<tr>
<td>Johnson B et al 1986</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 4 weeks of HCTZ 100 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Kuramoto et al 1981</td>
<td>RDBPCT meets criteria. 35 of the 44 patients in the trial treated with thiazide monotherapy. Trichlomethiazide 1-4 mg used and exact number of patients in each arm not given.</td>
</tr>
<tr>
<td>Langford et al 1990</td>
<td>HDFP trial reporting the end of the 5 year study findings of BP and metabolic data.</td>
</tr>
<tr>
<td>Lutterodt et al 1980</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 12 weeks of HCTZ 50 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given. Of the 27 patients 16 withdrew from the trial so drop out rate is more than 50%. The remaining 11 patients completed the trial.</td>
</tr>
<tr>
<td>Study</td>
<td>Details</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Materson et al 1995&lt;sup&gt;129&lt;/sup&gt;</td>
<td>Mean arterial BP data are given SBP and DBP data are not given. RDBPC trial included participants with DBP 95-109 mm Hg at baseline. HCTZ 12.5 mg/day or placebo was the intervention used but dose titrated in non-responders to achieve goal DBP &lt; 90 mm Hg. The data of all randomised patients on monotherapy are not given.</td>
</tr>
<tr>
<td>McCorvey et al 1993&lt;sup&gt;130&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria. HCTZ 25 mg/day for 3 days followed by HCTZ 50 mg/day for 4 weeks or placebo is the intervention used but data for 1&lt;sup&gt;st&lt;/sup&gt; 4 weeks of monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Milliez P et al 1975&lt;sup&gt;131&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 6 weeks of indapamide 5 mg/day, chlorthiazide 500 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given. WDAE is not given.</td>
</tr>
<tr>
<td>MRC group 1983&lt;sup&gt;132&lt;/sup&gt;</td>
<td>RDBPCT with bendrofluazide 5 mg/day, 10 mg/day or placebo given. However, number of patients in each treatment arm is not given.</td>
</tr>
<tr>
<td>Myers M et al 1982&lt;sup&gt;133&lt;/sup&gt;</td>
<td>RDBPCT. This trial meets the criteria but data on diuretic therapy were lumped together. No washout prior to double blind randomised treatment.</td>
</tr>
<tr>
<td>Myers M et al 1983&lt;sup&gt;134&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 6 weeks of HCTZ 50 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
</tr>
<tr>
<td>Okun R et al 1978&lt;sup&gt;135&lt;/sup&gt;</td>
<td>RDBPC trial. The trial meets the inclusion criteria with a 4</td>
</tr>
</tbody>
</table>
weeks wash out period followed by tricynafen 250 mg/day, HCTZ 50 mg/day or placebo treatment for 6 weeks. However dose titrated after 2 weeks in patients whose BP was not decreased by 10mm Hg.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olshan AR et al 1981&lt;sup&gt;136&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria, but data for 1&lt;sup&gt;st&lt;/sup&gt; month of furosemide 40 mg/day versus placebo monotherapy are valid to use per protocol requirement and is not given. Mean arterial BP data given at baseline and end of treatment with SBP and DBP data are not given individually.</td>
<td></td>
</tr>
<tr>
<td>Pearson R et al 1979&lt;sup&gt;137&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 6 weeks of tienilic acid 250 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
<td></td>
</tr>
<tr>
<td>Peterson et al 1996&lt;sup&gt;138&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 4 weeks of HCTZ 6 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
<td></td>
</tr>
<tr>
<td>Russel PR et al 1968&lt;sup&gt;139&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; 6 weeks of HCTZ 200 mg/day versus placebo monotherapy are valid to use per protocol requirement and are not given.</td>
<td></td>
</tr>
<tr>
<td>Salvetti et al 1989&lt;sup&gt;140&lt;/sup&gt;</td>
<td>This trial meets the inclusion criteria but BP data given as mean arterial BP and SBP and DBP could not be calculated individually based on the information in the trial.</td>
<td></td>
</tr>
<tr>
<td>Salvetti et al 1991&lt;sup&gt;141&lt;/sup&gt;</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1&lt;sup&gt;st&lt;/sup&gt; month of chlorthalidone 25 mg/day versus placebo monotherapy are valid to use per protocol requirement and are</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Seigel D et al 1990</td>
<td>This trial meets the inclusion criteria but data on SBP, DBP or metabolic effects or WDAE not given. Only data recorded are outcome on left ventricular hypertrophy on ECG. Seigel D et al 1992 using drug intervention therapy of HCTZ 50 mg/day, chlorthalidone 50 mg/day or placebo does not give actual BP values or metabolic data.</td>
<td></td>
</tr>
<tr>
<td>Stein CM et al 1992</td>
<td>RDBPC dose ranging cross-over trial in 19 black patients with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 6 weeks of HCTZ 6.25 mg/day, 12.5 mg/day, 25 mg/day, 50 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given.</td>
<td></td>
</tr>
<tr>
<td>Valmin K et al 1975</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 4 weeks of furosemide 12.5 mg/day, 25 mg/day, 40 mg/day or HCTZ 25 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given. WDAE is not given.</td>
<td></td>
</tr>
<tr>
<td>Valmin K et al 1979</td>
<td>RDBPC cross-over trial. Four weeks of placebo followed by 3 periods of 6 weeks of furosemide 40 mg b.i.d., 60 mg b.i.d. or 80 mg b.i.d. with intervening 4 weeks of placebo given in a random order. The washout period between treatment groups is not adequate to allow BP to come back to initial levels.</td>
<td></td>
</tr>
<tr>
<td>Weber JC et al 1977</td>
<td>RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for 1st 4 weeks of xipamid 20 mg/day, 40 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given. WDAE none.</td>
<td></td>
</tr>
</tbody>
</table>
Wilcox RG et al 1978 \textsuperscript{147}  

RDBPC cross-over trial with no washout period between active treatment. The trial does meet the inclusion criteria as drug therapy with bendrofluazide 5 mg/day, 10 mg/day or placebo monotherapy is given for 2 weeks and does not meet our criteria of a minimum of a 3 week period.

Wing LMH et al 1982 \textsuperscript{148}  

RDBPC cross-over trial with no washout period between active treatment. The trial meets the inclusion criteria but data for \textsuperscript{1st} 5 weeks of chlorthalidone 25 mg/day, chlorthalidone 50 mg/day and chlorothiazide 1000 mg/day or placebo monotherapy are valid to use per protocol requirement and are not given.

Wing LMH et al 1997 \textsuperscript{149}  

MCRDBPC cross over trial.. After \textsuperscript{1st} 2 weeks of double blind treatment with HCTZ 25 mg/day the dose was titrated to achieve a SBP of less than 160 mm Hg.

3.4. Overview of the trials meeting the inclusion criteria

Of the 2156 randomised controlled trials identified by the search strategy, only 36 trials (1.7\%) met the primary inclusion criteria and had data that could be extracted and analysed. Of these 36 trials, 33 trials compared thiazide and thiazide-related diuretics with placebo and three trials compared loop diuretics with placebo. 39 other trials met the primary inclusion criteria but were excluded because data were not reported in a way that could be used in this review.

It is important to note that the magnitude of the final effect size is calculated after the placebo effect has been subtracted (i.e. the change from the baseline in treatment group minus the change from baseline in the placebo group) and it represents the effect due to only the drug therapy.
3.5. Overview of the 33 trials using thiazide and thiazide-related diuretics as monotherapy in the treatment of primary hypertension

Table 5: Overview of the 33 trials of each drug within the thiazide and thiazide-related diuretic class

<table>
<thead>
<tr>
<th>Drug, dose range and total number of trials</th>
<th>No. of pts. in the treatment group</th>
<th>No. of pts. in the placebo group*</th>
<th>Mean age in years</th>
<th>Mean duration of treatment in weeks</th>
<th>Mean baseline BP(mm Hg)/pulse pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 3-100 mg/day</td>
<td>1238</td>
<td>889</td>
<td>53.2</td>
<td>9.6</td>
<td>159/101 58</td>
</tr>
<tr>
<td>15 trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTHD 12.5-450 mg/day</td>
<td>901</td>
<td>357</td>
<td>62.9</td>
<td>7.8</td>
<td>162/85 77</td>
</tr>
<tr>
<td>9 trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND 1.0-5.0 mg/day</td>
<td>615</td>
<td>399</td>
<td>57.9</td>
<td>8.0</td>
<td>157/98 59</td>
</tr>
<tr>
<td>6 trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYPTZ 50-500 µg/day</td>
<td>41</td>
<td>12</td>
<td>57</td>
<td>8.0</td>
<td>167/97 70</td>
</tr>
<tr>
<td>1 trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDFZ 1.25-10 mg/day</td>
<td>218</td>
<td>63</td>
<td>57.3</td>
<td>11.8</td>
<td>162/102 60</td>
</tr>
<tr>
<td>2 trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTZ 0.5-2.0 mg/day</td>
<td>78</td>
<td>27</td>
<td>NA</td>
<td>6.0</td>
<td>150/98 52</td>
</tr>
<tr>
<td>1 trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total = 33 trials*</td>
<td>3091</td>
<td>1720</td>
<td>57.1</td>
<td>8.8</td>
<td>159/97 62</td>
</tr>
</tbody>
</table>

* One trial by Siegel et al gave information only on metabolic data of both HCTZ and CTHD and it was only counted once. Also, the number of patients in the placebo group
is less than the treatment group, as the treatment group often included more than one dose of the drug.

3.6. Overview of the 3 trials using loop diuretics as monotherapy in the treatment of primary hypertension

Table 6: Overview of trials of each drug within the loop diuretic class

<table>
<thead>
<tr>
<th>Drug, dose range and total number of trials</th>
<th>No. of patients in treatment group</th>
<th>No. of patients in placebo group</th>
<th>Mean age in years</th>
<th>Mean duration of treatment in weeks</th>
<th>Mean baseline BP in mm Hg/Pulse pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide 60-80 mg/day 2 trials</td>
<td>45</td>
<td>45</td>
<td>55</td>
<td>6.7</td>
<td>172/106 66</td>
</tr>
<tr>
<td>Pirentanide 6 mg/day 1 trial</td>
<td>30</td>
<td>30</td>
<td>52.5</td>
<td>6</td>
<td>158/99 59</td>
</tr>
<tr>
<td>Total = 3 trials</td>
<td>75</td>
<td>75</td>
<td>54</td>
<td>6.4</td>
<td>168/104 64</td>
</tr>
</tbody>
</table>
3.7. Dose ranging blood pressure lowering efficacy of individual doses within the thiazide and thiazide-related diuretic class of drugs

Table 7: Data on the BP lowering efficacy of hydrochlorothiazide (HCTZ) 3 to 100 mg/day. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of HCTZ</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/day</td>
<td>1/22</td>
<td>-0.3(-7.3, 6.7)</td>
<td>1.7(-3.4, 6.8)</td>
</tr>
<tr>
<td>6 mg/day</td>
<td>1/22</td>
<td>-3.6(-9.9, 2.7)</td>
<td>-2.2(-6.4, 2.0)</td>
</tr>
<tr>
<td>12.5 mg/day</td>
<td>8/579</td>
<td>-5.7(-7.0, -4.5) *</td>
<td>-3.9(-4.7, -3.0) *</td>
</tr>
<tr>
<td>25 mg/day</td>
<td>7/368</td>
<td>-8.5(-10.4,-6.6) *</td>
<td>-4.7(-5.8,-3.5)*</td>
</tr>
<tr>
<td>50 mg/day</td>
<td>2/98</td>
<td>-9.1(-12.5, -5.7) *</td>
<td>-2.7(-4.9,-0.5) *</td>
</tr>
<tr>
<td>100 mg/day</td>
<td>2/92</td>
<td>-10.0(-13.6, -6.5) *</td>
<td>-3.8(-6.1,-1.6) *</td>
</tr>
</tbody>
</table>

* significant difference from placebo

HCTZ doses 3 to 6 mg/day did not show a significant decrease in BP compared to the placebo group. HCTZ doses 12.5 to 100 mg/day showed significant decreases in both SBP and DBP as compared to the placebo control group. The maximum dose at which the SBP lowering efficacy of HCTZ is approaching a maximum is between 12.5 and 25 mg/day. This conclusion was reached as the confidence intervals of all doses above HCTZ 12.5 mg/day overlap. The weighted mean baseline BP was 161/102 mm Hg in the HCTZ 25 mg/day and HCTZ 100 mg/day group and 176/103 mm Hg in the HCTZ 50 mg/day as compared to 153/101 mm Hg in the HCTZ 12.5 mg/day group. Therefore, the slightly greater SBP lowering effect at these higher doses could be partly explained by the higher baseline SBP levels.
Racial differences (percentage of black patients) in the trials at different doses could have affected the final effect size but this did not appear to be the case. Three of the 14 trials (Benz et al, Chrysant et al and MacKay et al) reported the percentage of black patients. 16.7% of patients were blacks in HCTZ 12.5 mg/day group compared to 20.4% patients in the HCTZ 25 mg/day group. The baseline BP in these trials were 153/102mm Hg. The overall percentage of blacks reported in HCTZ trials was 17.5%.

Sensitivity analyses after excluding trials with higher baseline SBP levels and comparing HCTZ 12.5 mg/day (SBP -5.6(-6.9, -4.4) mm Hg and DBP -3.2(-4.2, -2.3) mm Hg) with HCTZ 25 mg/day (SBP -6.4 (-9.0, -3.9) mm Hg and DBP -3.8 (-5.4, -2.2) mm Hg) showed that SBP and DBP lowering were not significantly different. It is clear that there is little or no increase in BP lowering for doses of HCTZ above 25 mg/day; therefore, the range from HCTZ 12.5 to 25 mg/day is the most useful range in the management of hypertension.

The overall estimate of the BP lowering efficacy of combining HCTZ doses 12.5 to 100 mg/day is SBP -7.0(-8.0, -6.0) mm Hg and DBP -4.0(-4.6, -3.3) mm Hg and for combined doses of HCTZ 25 to 100 mg/day is SBP -8.9(-10.4, -7.4) mm Hg and DBP -4.1 (-5.1, -3.2) mm Hg showed no significant difference between them. This is statistically significantly more than the 12.5 mg/day dose effect, suggesting that 12.5 mg is sub-maximal. This second mean is probably the best estimate of the maximal BP lowering effect of HCTZ 9/4 mm Hg. Figures 1 and 2 are included to show the SBP and DBP dose-response of HCTZ 3-100mg/day. Within the thiazide diuretic class of drugs, only HCTZ had data at low doses and gave a realistic dose-response curve. Therefore, for all other drugs only tabular data will be included.
Figure 1
SBP lowering dose response of HCTZ

+ SBP mm Hg

SBP (treatment-placebo) with 95% CI

Dose of HCTZ in mg/day
Figure: 2

DBP lowering dose response of HCTZ

\[\text{DBP mm Hg}\]

* confidence interval is narrow and could not be shown.
Table 8: Data on the BP lowering efficacy of chlorthalidone (CTHD) 12.5 to 450 mg/day. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of CTHD</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5-15 mg/day</td>
<td>3/133</td>
<td>-9.9(-12.8, -7.0)*</td>
<td>-3.1(-5.0, -1.1)*</td>
</tr>
<tr>
<td>25 mg/day</td>
<td>5/581</td>
<td>-14.1(-16.0, -12.3)*</td>
<td>-3.9(-5.1,-2.6)*</td>
</tr>
<tr>
<td>45-50 mg/day</td>
<td>4/114</td>
<td>-11.1(-14.1, -8.1)*</td>
<td>-4.8(-6.8, -2.7)*</td>
</tr>
<tr>
<td>75-450 mg/day</td>
<td>2/43</td>
<td>-7.9(-13.2, -2.7)*</td>
<td>-3.6(-6.9, -0.2)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

CTHD 12.5 to 450 mg/day showed a significant decrease in both SBP and DBP as compared to the placebo control group. The maximum dose at which the SBP lowering efficacy of CTHD is approaching maximum is between 12.5 and 25 mg/day. This conclusion was reached based on the fact that the confidence interval of all doses above CTHD 12.5 mg/day overlap. The weighted mean baseline SBP was 154 mm Hg in the CTHD 12.5 to 15 mg/day, CTHD 45-50mg/day and CTHD 75-450mg/day group as compared to 166 mm Hg in the CTHD 25 mg/day group. Therefore, the greater SBP lowering effect at CTHD 25 mg/day could be partly explained by the higher baseline SBP levels. Also, the racial differences (percentage of black patients) in the trials at different doses could have affected the final effect size, but this again did not seem to be the case. Five of the 8 trials (Materson et al, Morledge et al, Vardhan et al, Smith et al and Fernandez et al) reported the percentage of black patients. 13% of patients were blacks in CTHD 12.5-15 mg/day group, 19% in CTHD 25 mg/day group, 12.7% in the CTHD 50 mg/day group, and 25% in CTHD 75-450 mg/day group. The baseline BP
in these trials was 171/84 mm Hg. The overall percentage of blacks reported in CTHD trials was 18.5%. The weighted mean age of patients was similar in the CTHD 12.5-15 mg/day group (67.2 years) and in the CTHD 25 mg/day group (67.2 years).

Sensitivity analyses after excluding trials with higher baseline SBP levels and comparing CTHD 12.5-15 mg/day (SBP -9.0(-12.7, -5.3) mm Hg and DBP -3.0(-5.4, -0.7) mm Hg with CTHD 25 mg/day (SBP -11.0(-14.7, -7.4) mm Hg and DBP -4.2(-6.5, -1.8) mm Hg) showed that there was no significant difference between them. The range from CTHD 12.5 to 25 mg/day is the most common range used in the management of hypertension. The overall estimate of the BP lowering efficacy for combined CTHD doses of 25 to 450 mg/day is SBP -12.8(-14.3, -11.3) mm Hg and DBP -4.1 (-5.1, -3.0) mm Hg. This is not significantly greater than that for 12.5-15 mg/day dose SBP -9.9(-12.8, -7.0) and DBP -3.1(-5.0, -1.1). This suggests that the near maximum BP lowering efficacy of CTHD is achieved with 12.5 mg/day and the best estimate of the BP lowering effect of CTHD is the combined CTHD doses 12.5 to 450 mg/day for SBP -12.2(-13.5,-10.8) mm Hg and DBP -3.8(-4.7, -3.0) mm Hg. The systolic BP lowering effect appears to be greater than for other drugs.
Table 9: Data on the BP lowering efficacy of indapamide (IND) 1.0 to 5.0mg/day.

Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of IND</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg/day</td>
<td>1/22</td>
<td>-9.7(-17.0, -2.4)*</td>
<td>-3.0(-7.7, 1.7)</td>
</tr>
<tr>
<td>1.25 mg/day</td>
<td>3/309</td>
<td>-7.2(-9.3, -5.2)*</td>
<td>-3.7(-4.8, -2.5)*</td>
</tr>
<tr>
<td>1.5 mg/day</td>
<td>1/57</td>
<td>-9.4(-15.1, -3.7)*</td>
<td>-5.7(-9.0, -2.4)*</td>
</tr>
<tr>
<td>2.0 mg/day</td>
<td>1/55</td>
<td>-8.7(-14.7, -2.7)*</td>
<td>-3.6(-7.0, -0.2)*</td>
</tr>
<tr>
<td>2.5 mg/day</td>
<td>3/151</td>
<td>-8.5(-12.3, -4.7)*</td>
<td>-4.6(-6.8, -2.4)*</td>
</tr>
<tr>
<td>5.0 mg/day</td>
<td>1/21</td>
<td>-9.6(-17.0, -2.2)*</td>
<td>-4.0(-8.8, 0.8)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

IND 1.0 to 5.0 mg/day showed a significant decrease in SBP and IND 1.25 -5.0 mg/day shows a significant decrease in DBP as compared to the placebo control group. The dose at which the BP lowering efficacy of IND approaches maximum is 1.0 mg/day or less. This conclusion is reached as the confidence intervals of BP lowering at all doses equal to or above IND 1.0 mg/day overlap. The weighted mean baseline SBP was 153 mm Hg in the IND 1.0mg/day, IND 1.25 mg/day and in IND 5.0 mg/day group. The mean weighted baseline SBP in IND 1.5 mg/day, 2.0 mg/day and 2.5 mg/day was 165 mm Hg. Despite differences in the mean weighted baseline SBP in the IND group at various doses the decrease in SBP was similar at all doses and equal to the decrease at the lowest dose 1.0 mg/day. The percentages of blacks were reported in four of the six indapamide trials (Capone et al, Fiddes et al, Hall et al and Weilder et al). It was 26.7% in the IND 1.25 mg/day and 31% in IND 1.0 mg/day, IND 2.5 mg/day and
IND 5.0 mg/day. The overall percentage of blacks in all trials comparing indapamide with placebo was 27.3%. Also, the mean weighted age of patients in IND 1.25 mg/day group was 60.4 years compared to 53 years in all other groups using various indapamide doses.

Sensitivity analyses after excluding trials with higher baseline SBP levels (Fiddes et al) and comparing IND 1.0 mg/day (SBP -9.7(-17.0, -2.4) mm Hg and DBP -3.0(-7.7, 1.7) mm Hg with IND 1.25 mg/day (SBP -7.2(-9.6, -4.8) mm Hg and DBP -3.6(-5.0, -2.3) mm Hg showed that there was no significant difference between them. The overall estimate of the BP lowering efficacy of combined IND doses 1.0 to 5.0 mg/day is SBP -7.9(-9.5, -6.4) mm Hg and DBP -3.9(-4.8, -3.1) mm Hg and for combined IND doses 1.25 to 5.0 mg/day is (SBP -7.8(-9.5, -6.2) mm Hg and DBP -4.0(-4.9, -3.1) mm Hg showing that there is no significant difference between them. This proves that the minimum dose with the maximum SBP lowering efficacy of IND may be even lower than 1.0 mg/day. The best dose range for clinical use is 0.625 mg to 1.25 mg/day and the best estimate of the maximal blood pressure lowering effect is 8/4 mm Hg.
Table 10: Data on the BP lowering efficacy of cyclopenthiazide 50 to 500µg/day (CYPTZ). Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of CYPTZ</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg/day</td>
<td>1/13</td>
<td>-5.3(-15.0, 4.4)</td>
<td>-3.0(-9.2, 3.2)</td>
</tr>
<tr>
<td>125 µg/day</td>
<td>1/13</td>
<td>-12.0(-21.7, -2.3)*</td>
<td>-8.6(-14.6, -2.6)*</td>
</tr>
<tr>
<td>500 µg/day</td>
<td>1/13</td>
<td>-14.9(-24.6, -5.2)*</td>
<td>-7.0(-13.2, -0.8)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

A significant decrease in SBP and DBP was seen at doses 125 to 500 µg/day as compared to the placebo group. The dose range at which the SBP and DBP lowering efficacy of CYPTZ is approaching a maximum is between 50 to 125 µg/day. This conclusion was reached as the confidence interval of SBP and DBP lowering of CYPTZ 500 µg/day overlap. The overall and best estimate of the BP lowering efficacy of combined CYPTZ doses 125 to 500 µg/day is (SBP -13.5(-20.3, -6.6) mm Hg and DBP -7.8(-12.2, -3.5) mm Hg. This is a poor estimate due to the small number of patients as seen by the wide confidence intervals. More data in the dose range 50 to 250 µg/day are required to establish the dose-related BP lowering efficacy of CYPTZ.
Table 11: Data on the BP lowering efficacy of bendrofluazide (BDFZ) 1.25 to 10.0 mg/day. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of BDFZ</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 mg/day</td>
<td>2/62</td>
<td>-8.9(-13.2, -4.5)*</td>
<td>-5.9(-8.7, -3.1)*</td>
</tr>
<tr>
<td>2.5 mg/day</td>
<td>1/52</td>
<td>-10.9(-15.7, -6.1)*</td>
<td>-6.9(-10.0, -3.8)*</td>
</tr>
<tr>
<td>5.0 mg/day</td>
<td>1/52</td>
<td>-10.6(-15.4, -5.8)*</td>
<td>-6.2 (-9.3, -3.1)*</td>
</tr>
<tr>
<td>10.0 mg/day</td>
<td>1/51</td>
<td>-12.5(-17.3, -7.7)*</td>
<td>-7.0(-10.1, -3.9)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

BDFZ at doses 1.25 to 10 mg/day significantly reduced SBP and DBP as compared to the placebo control. The dose at which the SBP and the DBP lowering efficacy of BDFZ is approaching a maximum is 1.25 mg/day. This conclusion was reached based on the confidence intervals of all doses above 1.25 mg/day overlap. Therefore, data at doses below 1.25 mg/day are required to establish the dose-related BP lowering efficacy of BDFZ. The overall best estimate of the BP lowering efficacy for combined BDFZ doses 1.25 to 10 mg/day is SBP -10.6(-12.9, -8.3) mm Hg and DBP is -6.5(-8.0, -5.0) mm Hg.
Table 12: Data on the BP lowering efficacy of metolazone 0.5 to 2.0mg/day. Fixed
effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of MTZ</th>
<th>No. of trials/Total No. of patients in treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/day</td>
<td>1/26</td>
<td>-11.4(-18.1, -4.7)*</td>
<td>-5.9(-10.2, -1.6)*</td>
</tr>
<tr>
<td>1.0 mg/day</td>
<td>1/25</td>
<td>-11.6(-18.4, -4.9)*</td>
<td>-6.4(-10.7, -2.1)*</td>
</tr>
<tr>
<td>2.0 mg/day</td>
<td>1/27</td>
<td>-11.9(-18.5, -5.3)*</td>
<td>-5.2(-9.5, -1.0)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

MTZ 0.5 to 2.0 mg/day significantly reduced SBP and DBP as compared to the
placebo control group. The maximum dose at which BP lowering efficacy of MTZ is
approaching a maximum is 0.5 mg/day. Therefore, data on MTZ at doses below 0.5
mg/day are required to establish the dose-related BP lowering efficacy. The overall
best estimate of the BP lowering efficacy for combined MTZ doses 0.5 to 2 mg/day is
SBP -11.6(-15.5, -7.8) mm Hg and DBP is -5.8( -8.3, -3.4) mm Hg. This is a poor
estimate due to the small number of patients as seen by the wide confidence intervals.
Table 13: Data on the near maximum BP lowering efficacy of different thiazides.

Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of thiazide</th>
<th>No. of trials (Total No. of pts. in treatment vs placebo group)</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 25-100 mg/day</td>
<td>10/ (558 vs 598)</td>
<td>-8.9 (-10.4, -7.4)*</td>
<td>-4.1 (-5.1, -3.2)*</td>
</tr>
<tr>
<td>CTHD 12.5-450 mg/day</td>
<td>8/ (871 vs 535)</td>
<td>-12.2 (-13.5, -10.8)*</td>
<td>-3.8 (-4.7, -3.0)*</td>
</tr>
<tr>
<td>IND 1.0-5.0 mg/day</td>
<td>6/ (615 vs 559)</td>
<td>-7.9 (-9.5, -6.4)*</td>
<td>-3.9 (-4.8, -3.1)*</td>
</tr>
<tr>
<td>CYPTZ 125-500 μg/day</td>
<td>1/ (26 vs 24)</td>
<td>-13.5 (-20.3, -6.6)*</td>
<td>-7.8 (-12.2, -3.5)*</td>
</tr>
<tr>
<td>BDFZ 1.25-10 mg/day</td>
<td>2/ (218 vs 220)</td>
<td>-10.6 (-12.9, -8.3)*</td>
<td>-6.5 (-8.0, -5.0)*</td>
</tr>
<tr>
<td>MTZ 0.5-2.0 mg/day</td>
<td>1/ (78 vs 81)</td>
<td>-11.6 (-15.5, -7.8)*</td>
<td>-5.8 (-8.3, -3.4)*</td>
</tr>
<tr>
<td>All thiazide drugs</td>
<td>28/ (2365 vs 2017)</td>
<td>-10.0 (-10.8, -9.2)*</td>
<td>-4.3 (-4.8, -3.8)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

Comparison of the SBP lowering of different drugs within the thiazide and thiazide-related drug show that the SBP lowering of HCTZ, IND, CYPTZ, BDFZ and metolazone were not significantly different. However, CTHD (-12.2 mm Hg) lowered SBP significantly more than HCTZ (-8.9 mm Hg) and indapamide (-7.9 mm Hg).

Comparison of the DBP lowering of different drugs within the thiazide and thiazide-related drug show that the DBP lowering of HCTZ, CTHD, IND, CYPTZ, and metolazone were not significantly different. The only significant difference was that BDFZ (-6.5 mm Hg) lowered DBP significantly more than indapamide (-4.0 mm Hg). This is most likely a chance finding due to multiple comparisons.
The mean weighted baseline BP was 164/102 mm Hg in HCTZ 25-100 mg trials, 162/85 mm Hg in CTHD 12.5-450 mg trials and 157/98 mm Hg in the IND 1.0-5.0 mg trials. Although the baseline SBP was similar in all these trials, the pulse pressure was significantly greater in the CTHD trials as compared to HCTZ and IND trials.

Combining all trials of thiazide and thiazide-related diuretics at and above doses which approach the near maximum BP lowering effect gives the best estimate of the SBP lowering efficacy of thiazide diuretics, -10.0(-10.8, -9.2) mm Hg and DBP is -4.3(-4.8, -3.8) mm Hg.

3.8. Dose ranging blood pressure lowering efficacy of loop diuretics

Evidence relating to loop diuretics is very limited; therefore, a dose-related BP lowering effect could not be determined.

Table 14: Data on the BP lowering efficacy of furosemide. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of Furosemide</th>
<th>No. of trials/Total No. of pts. in the treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg/day</td>
<td>1/15</td>
<td>-10.0(-19.5, -0.5)*</td>
<td>-3.0(-9.1, 3.1)*</td>
</tr>
<tr>
<td>80 mg/day</td>
<td>1/30</td>
<td>-5.0(-11.3, 1.3)*</td>
<td>-8.0(-12.0, -4.0)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo
Table 15: Data on the BP lowering efficacy of piretanide. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of piretanide</th>
<th>No. of trials/Total No. of pts. in the treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg/day</td>
<td>1/30</td>
<td>-8.0(-14.3, -1.7)*</td>
<td>-4.2(-8.2, -0.2)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

Table 16: Data on the overall BP lowering efficacy of loop diuretics. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of loop diuretics</th>
<th>No. of trials/Total No. of pts. in the treatment group</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide 60-80 mg/day and piretanide 6 mg/day</td>
<td>3/75</td>
<td>-7.1(-11.1, -3.1)*</td>
<td>-5.6(-8.1, -3.0)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

In order to obtain the best estimate of the antihypertensive effect of loop diuretics, the results of these three trials can be combined. Loop diuretics significantly reduced SBP by -7.1(-11.1, -3.1) mm Hg and DBP by -5.6(-8.1, -3.0) mm Hg. It is clear from the wide confidence intervals that our knowledge of the BP lowering efficacy of loop diuretics as compared to placebo is uncertain.
3.9. BP lowering efficacy of low dose and high dose thiazide diuretics

Because we have established the clinical range of doses for each drug within the thiazide and thiazide-related diuretic drug class, we divided all trials into low dose, defined as the dose at which BP lowering was approaching near maximum response plus any dose approximately half the near maximal dose, and high-dose defined as all doses above the near maximum dose. The SBP and DBP lowering efficacy of each drug within the thiazide and thiazide-related diuretic class based on high- and low-dose were then compared.

The baseline BP in low-dose and high-dose trials for some drugs within the thiazide diuretic class were significantly different (for example in low-dose HCTZ trials the baseline BP was 157/101 mm Hg and in high-dose HCTZ trials it was 163/103 mm Hg; in low-dose CTHD trials the baseline BP was 157/101 mm Hg and in high-dose CTHD trials it was 163/84 mm Hg). Therefore, all trials with baseline SBP > 170 mm Hg were excluded and populations with similar mean weighted baseline BP and pulse pressure were then compared.
Table 17: Data on the BP lowering efficacy of low- and high-dose of different thiazide diuretic trials with similar baseline BP. Fixed effect model with 95% CI

<table>
<thead>
<tr>
<th>Dose of thiazide</th>
<th>No. of trials/ (total No. of patients in the treatment vs placebo group)</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose HCTZ 12.5-25 mg/day</td>
<td>8/ (806 vs 792)</td>
<td>-5.9(-7.0, -4.7)*</td>
<td>-3.8(-4.6, 3.1)</td>
</tr>
<tr>
<td>High-dose HCTZ 50-100 mg/day</td>
<td>1/ (10 vs 12)</td>
<td>-7.8(-18.2, 2.6)</td>
<td>1.1(-5.5, 7.7)</td>
</tr>
<tr>
<td>Low-dose CTHD 12.5-15 mg/day</td>
<td>2/ (86 vs 89)</td>
<td>-9.0(-12.7, -5.3)*</td>
<td>-3.0(-5.4, -0.7)*</td>
</tr>
<tr>
<td>High-dose CTHD 25-450 mg/day</td>
<td>6/ (210 vs 221)</td>
<td>-9.7(-12.1, -7.4)*</td>
<td>-4.7(-6.2, -3.2)*</td>
</tr>
<tr>
<td>Low-dose IND 1.0 mg/day</td>
<td>1/ (22 vs 22)</td>
<td>-9.7(-17.0, -2.4)*</td>
<td>-3.0(-7.7, 1.7)*</td>
</tr>
<tr>
<td>High-dose IND 1.25-5.0 mg/day</td>
<td>6/ (578 vs 525)</td>
<td>-7.8(-9.5, -6.2)*</td>
<td>-4.0(-4.9, -3.1)*</td>
</tr>
<tr>
<td>Low-dose CYPTZ 125 µg/day</td>
<td>1/ (13 vs 12)</td>
<td>-12.0(-21.7, -2.3)*</td>
<td>-8.6(-14.6, -2.6)*</td>
</tr>
<tr>
<td>High-dose CYPTZ 500 µg/day</td>
<td>1/ (13 vs 12)</td>
<td>-14.9(-24.6, -5.2)*</td>
<td>-7.0(-13.2, -0.8)*</td>
</tr>
<tr>
<td>Low-dose BDFZ 1.25 mg/day</td>
<td>1/ (62 vs 63)</td>
<td>-8.9(-13.2, -4.5)*</td>
<td>-5.9(-8.7, -3.1)*</td>
</tr>
<tr>
<td>High-dose BDFZ 2.5-10 mg/day</td>
<td>1/ (155 vs 156)</td>
<td>-11.3(-14.1, -8.6)*</td>
<td>-6.7(-8.5, -4.9)*</td>
</tr>
<tr>
<td>Low-dose MTZ 0.5 mg/day</td>
<td>1/ (26 vs 27)</td>
<td>-11.4(-18.1, -4.7)*</td>
<td>-5.9(-10.2, -1.6)*</td>
</tr>
<tr>
<td>High-dose MTZ 1-2 mg/day</td>
<td>1/ (52 vs 27)</td>
<td>-11.8(-16.5, -7.0)*</td>
<td>-5.8(-8.8, -2.8)*</td>
</tr>
<tr>
<td>Low-dose thiazide</td>
<td>14/ (1015 vs 1005)</td>
<td>-6.7(-7.8, -5.5)*</td>
<td>-4.0(-4.7, -3.2)*</td>
</tr>
<tr>
<td>High-dose thiazide</td>
<td>16/ (1018 vs 453)</td>
<td>-9.0(-10.2, -7.9)*</td>
<td>-4.6(-5.4, -3.9)*</td>
</tr>
<tr>
<td>Total (LD + HD)</td>
<td>2033 vs 1958</td>
<td>-7.9(-8.7, -7.0)*</td>
<td>-4.3(-4.8, -3.8)*</td>
</tr>
</tbody>
</table>

* significant difference from placebo

^ significant difference between low-dose and high-dose thiazide

For each drug in the thiazide diuretic class, the BP lowering efficacy at low-doses was similar to high-doses in trials with similar baseline BP. The overall best estimate of the
SBP lowering efficacy in the combined high-dose for all thiazide drugs was significantly (marginally) greater than the combined low-dose. This suggests that the maximum SBP lowering efficacy has not been reached with the combined low-doses of thiazide diuretics. The best overall estimate of BP lowering efficacy of thiazides in trials with similar baseline BP was 8/4 mm Hg.

3.10. Dose ranging withdrawal due to adverse events of thiazides and loop diuretics

3.10.1. Hydrochlorothiazide therapy versus placebo

One trial by Jounela et al reported no withdrawal due to adverse events in 22 patients in each of the HCTZ 3 mg/day group, HCTZ 6 mg/day group and the control group. Six of the eight trials reported 13 withdrawals of the 392 patients on HCTZ 12.5 mg/day compared to 8 withdrawals out of 390 patients in the placebo group RR 1.5(0.7, 3.3). Five of the seven trials reported 4 withdrawals out of 184 patients in the HCTZ 25 mg/day group compared to 3 withdrawal out of 223 patients in the placebo group with relative risk ratio (RR) 1.3(0.4, 4.0). Trials with HCTZ 50 mg/day and 100 mg/day did not report withdrawals due to adverse events. The risk ratio (RR) of 1.6(0.8, 3.4) withdrawal due to adverse events for combined HCTZ 3-25 mg doses was not significantly different in the active treatment (17/1620) and the placebo control (11/657) group.

3.10.2. Chlorthalidone therapy versus placebo

All three trials on CTHD 12.5-15 mg/day reported a total of 6 withdrawals out of the 133 patients in the treatment group compared to 7 withdrawals out of 129 patients in the placebo group RR 0.8(0.3, 2.2). Four of the five trials in the CTHD 25 mg/day reported 11 withdrawals out of 580 patients in the treatment group compared to 7
withdrawal out of 243 patients in the placebo group RR 1.4(0.60, 3.2). Three of the four
trials in the CTHD 50mg/day reported 9 withdrawals out of 79 patients group in the
treatment group compared to 5 withdrawal out of 77 patients in the placebo group RR
1.6(0.6, 4.0). Two trials in CTHD 75-450 mg reported 2 withdrawals out of 44 patients
in the treatment group compared to none out of 44 patients in the control group RR
3.00(0.3, 27.8). The RR of 1.1(0.6, 1.8) withdrawal due to adverse events for combined
CTHD 12.5-450 mg doses was not significantly different in the active treatment (28/827)
and the placebo control (19/487) group.

### 3.10.3. Indapamide therapy versus placebo

One trial reported no withdrawal due to adverse events in 22 patients in the
indapamide 1.0 mg/day group compared to 1 withdrawal out of 22 patients in the
placebo group RR 0.3(0.0, 7.8). Three trials reported 14 withdrawals out of the 312
patients on IND 1.25 mg/day compared to 13 withdrawals out of 309 patients in the
placebo group RR 1.1(0.5, 2.2). One trial reported 1 withdrawal out of 57 patients in
the IND 1.5 mg/day and IND 2.0 mg/day group compared to 1 withdrawal out of 58
patients in the placebo group RR 1.0(0.1, 16.5). Two of the three trials in the IND 2.5
mg/day reported 7 withdrawals out of 136 patients in the treatment group compared to
1 withdrawal out of 80 patients in the placebo group RR 3.1(0.5, 17.5). One trial
reported no withdrawals in either the placebo group (n =21) or the IND 5.0 mg/day
group (n = 22) with RR 1.1(0.0, 50.4). The RR of withdrawal due to adverse events
1.2(0.7, 2.3) for combined doses of indapamide was not significantly different in the
active treatment (23/603) and the placebo control (17/549) group.
3.10.4. Cyclopenthiazide therapy versus placebo

One trial by Mcveigh et al reported no withdrawals due to adverse events in 13 patients in the CYPTZ 50 µg/day group, 15 patients in the CYPTZ 125 µg/day group, 13 patients in the CYPTZ 500 µg/day group, and in 12 patients in the placebo group. The RR of withdrawal due to adverse events for combined CYPTZ 50-500 µg/day doses could not be estimated.

3.10.5. Bendrofluazide therapy versus placebo

One trial by Carlsen et al reported 2 withdrawals each in the BDFZ 1.25 mg/day group (n = 50), 2.5 mg/day group (n = 52) and in the 10 mg/day group (n = 51) and 1 withdrawal in the BDFZ 5 mg/day group (n = 52) compared to 2 withdrawals in the placebo group (n = 52). The RR 0.9(0.3, 2.4) of withdrawal due to adverse events for combined doses of BDFZ 1.25-10 mg was not significantly different in the active treatment (7/205) and the placebo control (8/208) group.

3.10.6. Metolazone therapy versus placebo

One trial by Curry et al reported no withdrawals in the metolazone 0.5mg/day group (n = 26), 1.0 mg/day group (n = 25) and in the 2.0 mg/day group (n = 27), compared to no withdrawals in the placebo group (n = 27). The RR of withdrawal due to adverse events for combined doses of metolazone 0.5-2.0 mg/day could not be estimated.

3.10.7. Furosemide therapy versus placebo control

One trial by Vadasz et al reported 1 withdrawal out of 15 patients in the furosemide 60 mg/day group compared to none out of 11 patients in the placebo group RR 3.0(0.1, 69.1). Also, only one trial by Werthiemer et al reported had no withdrawals in the furosemide 80 mg/day group (n = 30) and in the placebo group (n = 30). The RR
3.3(0.1, 78.5) of withdrawal due to adverse events for combined doses of furosemide was not significantly different in the active treatment (1/45) and the placebo (0/45) control group.

3.10.8. Piretanide therapy versus placebo control

One trial by Verho et al reported no withdrawals either in the piretanide 6 mg/day group (n = 30) or the placebo group (n = 30). The RR of withdrawal due to adverse events could not be estimated.

3.10.9. Overview of the withdrawal due to adverse effects for thiazide and loop diuretics

Because there was insufficient data to observe a dose-related response in withdrawal due to adverse drug effects in the thiazide diuretics, the next best thing to do was to combine them based on the classification according to the clinical range of doses, as low-dose and high-dose groups. Loop diuretics have insufficient data to divide them into low-or high-dose. The combined withdrawal due to adverse events of loop diuretics were one withdrawal out of 75 patients in the treatment group versus none out of 75 patients in the placebo group RR 3.0(0.1, 71.9).
Table 18: Withdrawal due to adverse drug effects for each drug in the thiazide diuretic trials at low- and high-doses.

<table>
<thead>
<tr>
<th>Thiazide diuretic drug</th>
<th>Low-dose Treatment vs placebo RR with 95% CI</th>
<th>High-dose Treatment vs placebo RR with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>17/576 vs 11/613 1.7(0.8, 3.5)</td>
<td>No data</td>
</tr>
<tr>
<td>Chloorthalidone</td>
<td>6/133 vs 7/129 0.8(0.3, 2.5)</td>
<td>22/694 vs 12/364 1.0(0.5, 2.0)</td>
</tr>
<tr>
<td>Indapamide</td>
<td>0/22 vs 1/22 0.1(0, 6.8)</td>
<td>23/581 vs 16/527 1.3(0.7, 2.5)</td>
</tr>
<tr>
<td>Cyclopenthiazide</td>
<td>0/15 vs 0/12 Cannot be estimated</td>
<td>0/13 vs 0/12 Cannot be estimated</td>
</tr>
<tr>
<td>Bendrofluazide</td>
<td>2/50 vs 2/52 1.0(0.1, 7.6)</td>
<td>5/155 vs 6/156 0.8(0.3, 2.8)</td>
</tr>
<tr>
<td>Metolazone</td>
<td>0/26 vs 0/27 Cannot be estimated</td>
<td>0/52 vs 0/54 Cannot be estimated</td>
</tr>
<tr>
<td>Combined withdrawals</td>
<td>25/822 vs 21/855 1.2(0.7, 2.2)</td>
<td>50/1495 vs 34/1113 1.1(0.7, 1.7)</td>
</tr>
<tr>
<td>(LD + HD) thiazide</td>
<td>75/2317 vs 55/1962 1.1(0.8, 1.6)</td>
<td></td>
</tr>
</tbody>
</table>

These data show that the withdrawal due to adverse drug effects were similar to placebo control group for each drug at low- and high-dose. Also combining low-doses
or high-doses of different drugs in the thiazide diuretic class show no significant difference in patient withdrawals as compared to the placebo group.

Combining withdrawal due to adverse drug effects for all thiazide drugs shows no significant difference as compared to the placebo group RR 1.1(0.8, 1.6).

3.11. **Dose ranging metabolic effects of thiazides and loop diuretics**

The data on metabolic adverse events (serum potassium, glucose, uric acid, creatinine, triglycerides and total cholesterol levels) were reported in 15 trials using thiazide monotherapy and in only one trial using furosemide 80 mg/day monotherapy. There are insufficient data to observe dose-related metabolic adverse events; therefore, doses have been combined together as low-dose and high-dose thiazide trials. Data on loop diuretics are insufficient for any kind of classification.
Table 19: Metabolic adverse effects of low-dose and high-dose thiazide diuretics on serum potassium, uric acid and creatinine levels.

<table>
<thead>
<tr>
<th>Thiazide drug</th>
<th>Serum potassium in mmol/L</th>
<th>Serum uric acid mmol/L</th>
<th>Serum creatinine μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5-25 mg &amp; HCTZ 50-100 mg</td>
<td>-0.12(-0.23,-0.02)*</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>CTHD 12.5-15mg &amp; CTHD 25-450 mg</td>
<td>-0.38(-0.50, -0.26)*</td>
<td>0.05(0.02, 0.08)*</td>
<td>No data</td>
</tr>
<tr>
<td>IND 1.0 mg &amp; IND 1.25-5.0 mg</td>
<td>-0.11(-0.38, 0.16)</td>
<td>0.04(-0.01, 0.09)</td>
<td>No data</td>
</tr>
<tr>
<td>CYPTZ 125 μg &amp; CYPTZ 500 μg</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>BDFZ 1.25 mg &amp; BDFZ 2.5-10 mg</td>
<td>-0.25(-0.42, -0.08)*</td>
<td>No data</td>
<td>5.10(0.66, 9.60)</td>
</tr>
<tr>
<td>MTZ 0.5 mg &amp; MTZ 1-2 mg</td>
<td>-0.15(-0.41, -0.11)*</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Thiazide (LD) &amp; Thiazide (HD)</td>
<td>-0.22(-0.29, -0.16)*</td>
<td>0.05(0.02, 0.07)*</td>
<td>5.10(-0.66,9.6)</td>
</tr>
<tr>
<td>(No. of pts. in LD) &amp; (No. of pts. in HD)</td>
<td>(N = 315)</td>
<td>(N = 107)</td>
<td>(N = 50)</td>
</tr>
<tr>
<td>LD + HD) &amp; LD + HD)</td>
<td>-0.42(-0.46, -0.38)*</td>
<td>0.05(0.04, 0.06)*</td>
<td>0.9(0.74, 1.02)*</td>
</tr>
<tr>
<td>(No. of pts.)</td>
<td>(N = 1427)</td>
<td>(N =472)</td>
<td>(N = 308)</td>
</tr>
<tr>
<td>Baseline values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD &amp; HD</td>
<td>4.3 mmol/L</td>
<td>0.39 mmol/l</td>
<td>78.6 μmol/L</td>
</tr>
<tr>
<td>(LD + HD)</td>
<td>4.3 mmol/L</td>
<td>0.35 mmol/l</td>
<td>90.3 μmol/L</td>
</tr>
<tr>
<td>Normal values</td>
<td>3.5-5.0 mmol/L</td>
<td>0.12-0.44 mmol/L</td>
<td>88-132 μmol/L</td>
</tr>
</tbody>
</table>

* significant difference from placebo

^ significant difference between low-dose and high-dose thiazide
Table 20: Metabolic adverse effects of low-dose and high-dose thiazide diuretics on serum glucose, triglycerides and total cholesterol.

<table>
<thead>
<tr>
<th>Thiazide drug</th>
<th>Low-dose/day &amp; High-dose/day</th>
<th>Serum glucose mmol/L</th>
<th>Serum triglyceride mmol/L</th>
<th>Serum total Cholesterol mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ 12.5-25 mg</td>
<td>HCTZ 50-100 mg</td>
<td>-0.01 (-0.33, 0.30)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>CTHD 12.5-15 mg</td>
<td>CTHD 25-450 mg</td>
<td>0.49 (0.13, 0.86)*</td>
<td>No data</td>
<td>0.37 (0.09, 0.65)*</td>
</tr>
<tr>
<td>IND 1.0 mg</td>
<td>IND 1.25-5.0 mg</td>
<td>-0.11 (-1.43, 1.21)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>CYPTZ 125 µg</td>
<td>CYPTZ 500 µg</td>
<td>No data</td>
<td>0.40 (-0.58, 1.38)</td>
<td>0.90 (-1.06, 2.9)</td>
</tr>
<tr>
<td>BDFZ 1.25 mg</td>
<td>BDFZ 2.5-10 mg</td>
<td>-0.11 (-0.38, 0.16)</td>
<td>0.13 (-0.22, 0.48)</td>
<td>0.03 (-0.25, 0.31)</td>
</tr>
<tr>
<td>MTZ 0.5 mg</td>
<td>MTZ 1-2 mg</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Thiazide (LD) (No. of pts. in LD)</td>
<td>(N = 202)</td>
<td>0.06 (-0.11, 0.24)</td>
<td>0.16 (-0.17, 0.49)</td>
<td>0.21 (0.01, 0.40)* (N = 129)</td>
</tr>
<tr>
<td>Thiazide (HD) (No. of pts. in HD)</td>
<td>(N = 63)</td>
<td>0.23 (0.01, 0.35)*</td>
<td>0.26 (0.24, 0.27)*</td>
<td>0.20 (0.09, 0.31)* (N = 449)</td>
</tr>
<tr>
<td>(LD + HD) (No. of pts.)</td>
<td>(N = 816)</td>
<td>0.19 (-0.05, 0.42)</td>
<td>0.24 (0.23, 0.25)*</td>
<td>0.20 (0.06, 0.35)* (N = 578)</td>
</tr>
<tr>
<td>Baseline values</td>
<td></td>
<td>5.4 mmol/L</td>
<td>1.6 mmol/l</td>
<td>6.1 mmol/L</td>
</tr>
<tr>
<td>LD HD</td>
<td>(LD + HD) Normal range</td>
<td>5.3 mmol/L</td>
<td>1.0 mmol/l</td>
<td>4.5 mmol/L</td>
</tr>
<tr>
<td>5.4 mmol/L</td>
<td>1.1 mmol/l</td>
<td>4.9 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1-5.8 mmol/L</td>
<td>0.56-1.69 mmol/L</td>
<td>4.1-6.0 mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* significant difference from placebo

^ significant difference between low-dose and high-dose thiazide
Table 19 and 20 show that the overall combined doses (low- and high-dose) of different drugs within the thiazide diuretic class show statistically significant metabolic adverse effects compared to placebo. Significantly lower serum potassium and a significantly higher serum uric acid, creatinine, triglycerides and total cholesterol were observed compared to placebo.

Comparing combined high-doses to low-doses of different drugs in the thiazide diuretic class showed that high-dose had significantly decreased serum potassium levels compared to low-dose thiazides.

Table 21: Metabolic adverse drug effects of loop diuretics based on only one trial with furosemide 80mg/day.

<table>
<thead>
<tr>
<th>Furosemide 80 mg/day</th>
<th>Metabolic adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium mmol/L</td>
<td>-0.15(-0.38, 0.08)</td>
</tr>
<tr>
<td>Serum uric acid mmol/L</td>
<td>0.11(0.05, 0.17)*</td>
</tr>
<tr>
<td>Serum creatinine µmol/L</td>
<td>No data</td>
</tr>
<tr>
<td>Serum glucose mmol/L</td>
<td>0.11(-1.09, 1.31)</td>
</tr>
<tr>
<td>Serum triglyceride mmol/L</td>
<td>No data</td>
</tr>
<tr>
<td>Serum total cholesterol mmol/L</td>
<td>No data</td>
</tr>
</tbody>
</table>

* significant difference from placebo
4. DISCUSSION

First-line thiazide diuretics have been proven to reduce morbidity and mortality in the treatment of hypertension. This is well demonstrated in two systematic reviews of first-line treatment of hypertension. (Wright\textsuperscript{57} et al and Psaty\textsuperscript{150} et al). All randomised controlled trials, at least one year in duration, reporting mortality and morbidity outcomes in patients with primary hypertension using first-line antihypertensive therapy (thiazides, beta-blockers, ACE inhibitors, alpha adrenergic blockers, angiotensin receptor blockers and calcium channel blockers) were included. In these trials, the dose of thiazide could be titrated and other drugs added if blood pressure was not lowered to a defined target.

A meta-analysis of blood pressure lowering efficacy of these trials showed that first-line low-dose thiazide therapy (mean dose of HCTZ 26 mg or equivalent) significantly reduced SBP by 15.9 (99% CI -16.8, -14.9) mm Hg and DBP by 6.5 (99% CI -6.8, - 6.2) mm Hg as compared to an untreated control. Low-dose thiazides also significantly reduced death (RR 0.89 with 95% CI 0.81, 0.99), stroke (RR 0.66 with 95% CI 0.56, 0.79), coronary heart disease (RR 0.72 with 95% CI 0.61, 0.85) and total cardiovascular events (RR 0.69 with 95% CI 0.63, 0.77). First-line high-dose thiazide therapy (mean dose of HCTZ 90 mg or equivalent) significantly reduced SBP by 13.9 (99% CI -14.6, -13.1) mm Hg and DBP by 7.0 (99% CI -7.4, - 6.5) mm Hg as compared to an untreated control. High-dose thiazides significantly reduced stroke (RR 0.49 with 95% CI 0.38, 0.62) and total cardiovascular events (RR 0.72 with 95% CI 0.63, 0.82). However, no significant effect on death (RR 0.90 with 95% CI 0.76, 1.05) or coronary heart disease (RR 1.0 with 95% CI 0.84, 1.19) was seen. This suggests that BP lowering as a surrogate outcome is insufficient to predict effects on all outcomes.
Although low-dose and high-dose first-line thiazides reduced SBP and DBP to a similar extent, their effect on coronary heart disease events appeared to be different. These findings lead to a number of questions. Is the blood pressure lowering effect of low-dose thiazides really the same as that produced by high-dose thiazides? What is the dose-response relationship of thiazides in terms of blood pressure lowering? Do thiazides have adverse consequences at high doses that do not occur at low-doses? To find answers to these questions it becomes important to know the dose-response relationship for various effects of thiazides. This systematic review aimed to better define the dose-response relationships of thiazides and to determine the lowest dose with near maximum BP lowering efficacy for each diuretic within the thiazide and thiazide-related class of drugs.

BP lowering by thiazides and thiazide-related diuretics is believed to be due to natriuresis and possibly also vasodilatation. Loop diuretics are also believed to lower BP due to natriuresis. Do diuretics acting by other mechanisms of action on the kidney such as loop diuretics also lower blood pressure? Does the difference in mechanism of action on the kidney have an effect on the magnitude of BP lowering of these two classes of drugs? The dose-related BP lowering efficacy of loop diuretics has not been studied. It is also important to mention that the effectiveness of loop diuretics in terms of reduction in death, stroke, coronary heart disease or total cardiovascular events has also not been studied.
4.1. What is the dose-related BP lowering efficacy of each drug within the thiazide and thiazide-related diuretic class and what is the best estimate of the magnitude of the BP lowering effect?

This systematic review evaluated 32 trials involving 4699 patients (3006 patients in the treatment group and 1693 patients in the placebo control group), (mean age of 57 years, mean duration of treatment 8.8 weeks and mean baseline BP of 159/97 mm Hg) on thiazide monotherapy.

The dose-related BP lowering efficacy of HCTZ 3-100 mg/day showed a significant difference from placebo group at HCTZ doses ≥ 12.5 mg/day. HCTZ 25 mg/day was the lowest dose of HCTZ approaching the maximum BP lowering efficacy. Combining doses of HCTZ of 25 mg and above gives the best estimate of average BP lowering and the magnitude of the effect is 8.9/4.1 mm Hg. (Table 7)

The dose-related BP lowering efficacy of CTHD 12.5-450 mg/day showed a significant difference from placebo group at all CTHD doses ≥ 12.5 mg/day. CTHD 12.5 mg/day is the lowest dose in the CTHD group approaching the maximum BP lowering effect. Combining doses of CTHD of 12.5 mg and above gives the best estimate of average BP lowering and the magnitude of effect is 12.2/3.8 mm Hg. (Table 8)

The dose-related BP lowering efficacy of IND 1.0-5.0 mg/day showed a significant difference from placebo group at IND doses ≥ 1.0 mg/day. Indapamide 1.0 mg/day was the lowest dose in the IND group approaching the maximum BP lowering effect. Combining doses of IND 1.0 mg/day and above gives the best estimate of average BP lowering and the magnitude of effect is 7.9/3.9 mm Hg. (Table 9)
The dose-related BP lowering efficacy of CYPTZ 50-500 μg/day showed a significant difference from placebo group at CYPTZ doses > 50 μg/day. CYPTZ 125 μg/day was the lowest dose in the CYPTZ group approaching the maximum BP lowering effect. Combining doses of CYPTZ 125 μg and above gives the best estimate of average BP lowering and the magnitude of effect is 13.5/7.8 mm Hg. (Table 10)

The dose-related BP lowering efficacy of BDFZ 1.25-10.0 mg/day showed a significant difference from placebo group at BDFZ doses ≥ 1.25 mg/day. BDFZ 1.25 mg/day was the lowest dose in the BDFZ group approaching the maximum BP lowering effect. Combining doses of BDFZ 1.25-mg and above gives the best estimate of average BP lowering and the magnitude of effect is 10.6/6.5 mm Hg. (Table 11)

The dose-related BP lowering efficacy of MTZ 0.5-2.0 mg/day showed a significant difference from placebo group at MTZ doses ≥ 0.5 mg/day. MTZ 0.5 mg/day is the lowest dose in the MTZ group approaching the maximum BP lowering effect. Combining doses of MTZ 0.5 mg and above gives the best estimate of average BP lowering and the magnitude of effect is 11.6/5.8 mm Hg. (Table 12)

This systematic review identified the doses of thiazide and thiazide-related diuretics that were shown to approach the near maximum BP lowering efficacy. They are HCTZ 25 mg/day, CTHD 12.5 mg/day, IND 1.0 mg/day, CYPTZ 125 μg/day, BDFZ 1.25 mg/day and metolazone 0.5 mg/day.

4.2. Is there a significant difference in the best estimate of the magnitude of the SBP and the DBP lowering effect of different drugs within the diuretic class of drugs?

Comparison of the SBP lowering of different drugs within the thiazide and thiazide-related drug shows that the SBP lowering of HCTZ, IND, CYPTZ, BDFZ and
metolazone were not significantly different. (Table 13). However, CTHD -12.8 (-14.3, -11.3) mm Hg lowered SBP significantly more than HCTZ -8.9 (-10.4, -7.4) mm Hg and indapamide -7.8(-9.5, -6.2) mm Hg.

4.3. *Is the SBP lowering efficacy of CTHD greater than HCTZ and IND? Is this a chance finding or is it due to the difference in population baseline characteristics?*

The mean weighted baseline BP in HCTZ trials was 164/102 mm Hg, in CTHD trials was 162/85 mm Hg and in the IND trials was 157/98 mm Hg. Although the baseline SBP in all the groups was similar, the baseline pulse pressure in the CTHD group (77) was significantly greater than the HCTZ group (62) and the IND group (59).

The difference in the SBP lowering efficacy of CTHD trials may be either due to the greater capacity of CTHD to lower SBP as compared to HCTZ and IND or due to a different population group being compared. It is probably true that the ability to lower SBP is also dependent on the pulse pressure. Therefore, we conclude that despite CTHD having a statistically greater effect on lowering systolic pressure, it is most likely because the population was different and that the two drugs are not different. It is probable that CTHD is equal in maximal SBP lowering effect to all thiazides. To definitively answer this question, a head to head trial comparing equipotent doses of HCTZ 12.5 to 50 mg/day and CTHD 6 to 25 mg/day should be done.

4.4. *Is the DBP lowering efficacy of BDFZ greater than CTHD and IND?*

Is this difference real or a chance finding? This evidence should be interpreted carefully, as it is weak evidence in terms of indirect comparison of (BDFZ versus
placebo group to CTHD and IND versus placebo group). This could result from multiple comparisons between groups. Moreover, the effect size in the BDFZ group is based largely on one trial by Carlsen et al. More trials with BDFZ need to be done to have a better estimate of the diastolic BP lowering effect of this drug.

4.5. What is the best overall estimate of the BP lowering efficacy of thiazide diuretics?

Because no significant difference was found in the magnitude of the effect size between various drugs within the thiazide diuretic class, we combined all the trials of thiazide and thiazide-related diuretics at and above doses which approach the near maximum BP lowering effect. The best overall estimate of the BP lowering efficacy of the combined doses of all drugs in the thiazide diuretic class is 10.0/4.3 mm Hg. (Table 13) It is of potential clinical significance that this overall estimate represents approximately 2/3\textsuperscript{rd} of the BP lowering effect seen in the morbidity and mortality trials where thiazides were used as first-line treatment (15.2/6.9 mm Hg).\textsuperscript{57}

4.6. What is the magnitude of the BP lowering of each drug within the thiazide and thiazide-related diuretic class at low- and high-dose? Is there a significant difference in the magnitude of the BP lowering effect at low- and high-dose?

Based on the clinical range of doses lowering BP in thiazide trials, we divided the trials into low-dose and high-dose thiazide trials. Low-dose was defined as the dose at which the BP lowering was approaching the maximal response (near maximal dose) plus any doses approximately half the near maximal dose. High-dose was defined as all doses above the near maximal dose.
Comparison of the BP lowering of low- and high-dose of each drug within the thiazide and thiazide-related drug class for trials with similar baseline BP shows that there is a greater BP lowering effect at the defined high doses overall than the defined low doses but the magnitude of this difference is small. (Table 17)

4.7. Do thiazides have dose-related adverse drug effects that lead to withdrawal of patients from the trials during 3-12 weeks of monotherapy?

Because data on withdrawal due to adverse drug effects were insufficient to examine a dose-related withdrawal response, we combined them as withdrawals in low-dose trials and high-dose trials. (Table 18). There was no significant difference in withdrawal due to adverse effects in low dose or high-dose trials compared to placebo control. Combining the withdrawal due to adverse drug effects of different drugs within the thiazide diuretic class in all trials showed a RR of 1.2(0.7, 2.2), which was not significantly different from placebo group. Thus, this systematic review confirms that thiazide diuretic monotherapy for 3-12 weeks duration is not associated with more withdrawals due to adverse drug effects than placebo.

4.8. Do thiazides have dose-related metabolic adverse drug effects during 3-12 weeks of monotherapy?

Because data on metabolic adverse effects of thiazide and thiazide-related diuretic are not sufficient to examine a dose-related response, we combined the metabolic adverse effects in low-dose trials and high-dose trials. (Table 19 and 20) Overall, combined low and high doses of thiazides significantly decreased serum potassium levels and significantly increased serum uric acid, creatinine, triglycerides and cholesterol levels compared to placebo control. Comparing combined high-doses
to low-doses of different drugs in the thiazide diuretic class showed that the high-dose group significantly lowered serum potassium level as compared to the low-dose group. These effects were seen in a short duration of 3-12 weeks.

The next best way to obtain information on long-term adverse effects due to thiazide and thiazide-related diuretics is to study large trials with a longer duration of treatment giving this information. However, this was not the objective of this systematic review.

This systematic review demonstrates that the BP lowering efficacy was similar at low- and high-dose but metabolic adverse effects were greater at high dose. Therefore, there is little to be gained by using high doses of thiazides. In addition other reviews have shown that lower doses achieves optimal reduction in mortality and morbidity. 5, 57

4.9. What is the overall dose-related BP lowering efficacy of thiazide diuretics?

The dose-related BP lowering effects of each drug within the thiazide, thiazide-related diuretics and loop diuretic is examined by this systematic review. This review has established that the lowest range of clinically recommended doses of thiazide and thiazide-related diuretics are approaching the dose which has a near maximum BP lowering effect. Trials with doses of HCTZ less than 12.5 mg/day, CTHD less than 12.5 mg/day, IND less than 1.0 mg/day, CYPTZ less than 50 μg/day, BDFZ less than 1.25 mg/day and metolazone less than 0.5 mg/day are required to better define the dose-response relationship and to allow the calculation of an ED50. An ED50 would be the best way to directly compare the potency of the different drugs in the clinical setting.

The mean weighted baseline BP in all thiazide and thiazide-related diuretic trials was 159/97 mm Hg and the overall BP lowering efficacy for doses at and above those
approaching maximum was 10.0/4.3 mm Hg. This mean effect size can also be expressed as a percentage of the decrease in BP relative to the baseline. This calculation shows the mean percentage decrease in SBP was 6.3% and DBP was 4.4%.

4.10. Does monotherapy with thiazide diuretics for 3-12 weeks reduce pulse pressure in patients with primary hypertension?

The data in this systematic review demonstrate that thiazide diuretics reduce the BP by 10/4 mm Hg and hence reduce pulse pressure by 6 mm Hg compared to the baseline pulse pressure. The decrease in pulse pressure expressed as a percentage is 9.7%.

4.11. Why does the maximum BP lowering effect of thiazides occur over such a narrow range of doses and then appear to reach a maximum?

One possible factor involved is the operation of other physiological mechanisms in the body such as the renin-angiotensin-aldosterone and adrenergic systems that counteracts the BP lowering effect. This has important implications for the management of hypertension. It strongly suggests that there is little to be gained by using high-doses of thiazides. We suggest from these data that HCTZ dose could be titrated to a maximum of 25 mg/day, CTHD to a maximum of 12.5 mg/day, IND to a maximum of 1.0 mg/day. At that point, a second drug (that would blunt the adaptive process induced by thiazides) from a different first-line antihypertensive therapy should be added if further reduction in BP is desired.

Because data are limited to a small number of trials for CYPTZ and metolazone, we do not have much confidence in the effect size and future trials at various doses should be done to determine the dose with maximum BP lowering efficacy for these
drugs and plethora of the other thiazide drugs (chlorothiazide, buthiazide, hydroflumethiazide, trichloromethiazide, methylclothiazide, polythiazide, cyclothiazide, quinethazone, fenquizone, clorexolone, clopamide, diapamide, isodapamide, mefruside and xipamide) for which we found no data.

4.12. What could be the possible reasons that would lead to underestimation or overestimation of the magnitude of BP lowering effect in this systematic review?

Publication bias is the bias introduced in a systematic review due to only positive studies being accepted for publication and negative studies remaining unpublished. There is a risk of publication bias and this could not be assessed in this review. However, because thiazides were first introduced for treatment of fluid overload and their antihypertensive action was noticed subsequently, it is our opinion that publication bias based on the BP lowering effect is less likely than if they had initially been introduced as antihypertensives.

Trials sponsored by pharmaceutical companies are more subject to publication bias but this could not be assessed and it would be very difficult to identify old unpublished trials at this time. In this systematic review 39% of all included trials were sponsored by industry.\textsuperscript{151}

The method by which BP was measured varied in different trials and in different settings and inter- and intra-observer bias could be a possibility. If the blinding of the individual measuring BP was not maintained, the effect size may be an overestimate. Unblinding of the patient to active or placebo therapy is a likely possibility, as patients on diuretic drugs might have noticed initial increased urine output in the first few days and might correctly guess whether they were on active treatment or placebo. The drop-
out rates of patients in the trial was very low so this should not have had an effect on the effect size.

Quality of the trials based on Jadad score showed 20/36 (55.6%) trials were good quality trials and 16/36 (44.4%) were of poor quality. A sensitivity analysis based on quality did not show an effect in this review.

Underestimation of the effect of drug therapy is possible if compliance was poor. This was not reported in most trials. We have assumed a relatively high compliance rate due to the careful monitoring of the patients and the relatively short duration of these trials.

4.13. Do diuretics acting at a different anatomical site on the kidney such as loop diuretics also lower blood pressure? Does the difference in mechanism of diuretic action have an effect on the magnitude of BP lowering of these two classes of drugs? Does the data in this systematic review help to explain the mechanism of the blood pressure lowering effect of thiazide and loop diuretics?

Evidence relating to loop diuretics is very limited. Due to lack of data, interpretation relating to either dose-related BP lowering efficacy, withdrawal due to adverse drug effects or metabolic adverse effects cannot be made. In order to obtain the best estimate of the antihypertensive effect of loop diuretics, the results of the three available trials were combined. Loop diuretics significantly reduced SBP by -7.1(-11.1, -3.1) mm Hg and DBP by -5.6(-8.1, -3.0) mm Hg. The relative risk of withdrawal due to adverse drug effects for loop diuretics was not significantly different than the placebo control group 3.0(0.1, 71.9). Metabolic adverse effects were available in only one trial using furosemide 80 mg/day. Due to the small amount of data and the wide confidence
intervals for loop diuretics, we are not confident about the effect size. It is surprising that furosemide and torasemide are indicated for the treatment of high blood pressure in Canada with this paucity of evidence of BP lowering efficacy in the published literature.

One of the goals of this systematic review was to compare the BP lowering effect of thiazides and loop diuretics to possibly explain whether the lowering of BP could be explained by natriuresis. If thiazides and loop diuretics lowered BP to a similar extent or if loop diuretics lower BP more than thiazides then the mechanism of BP lowering could be purely due to their natriuretic effect. However, if thiazides lowered BP to a greater extent than loop diuretics it would suggest that other mechanisms are involved. However, since data on loop diuretics was insufficient to have any confidence in their magnitude of BP lowering, we were unable to answer this question. Cross-over studies and head-to-head trials would be the next logical step in testing the magnitude of BP lowering of thiazides and loop diuretics.

The data in this thesis demonstrated that thiazides reduced SBP to a greater extent than DBP in terms of an absolute decrease in mm Hg as well as a percentage decrease as compared to the baseline values. Moreover the effect of thiazides on decreasing pulse pressure expressed as a percentage is greater than on SBP and DBP. We know that BP is a product of cardiac output and peripheral resistance. If BP was reduced purely due to an effect on peripheral resistance then a similar percentage of decrease in systolic as well as the diastolic BP and a small effect on pulse pressure would be expected. Since this was not seen with thiazides, we have to assume that effect of thiazides is not primarily on peripheral resistance and must be on cardiac output. The cardiac output depends on heart rate and stroke volume and stroke
volume is dependent upon cardiac contractility and venous return. Since there is no
evidence that thiazides affect the heart rate or cardiac contractility they must be
affecting venous return. Venous return could be decreased by either a decrease in
plasma volume due to diuresis or an increase in capacitance (venous and/or arterial).
A decrease in vascular volume has been noted as a short term effect with thiazides,
however in long term studies a decrease could not be detected. In my opinion it is
most likely that the chronic mechanism of blood pressure lowering effect of thiazides is
due to an increase in capacitance.

This potential property of increasing capacitance of thiazides may be very
important in terms of their long term beneficial effects in reducing cardiovascular
morbidity and mortality. In the Syst-Eur trial\cite{Syst-Eur} antihypertensive therapy using a calcium-
channel blocker, nitrendipine as the first-line drug in patients with isolated systolic
hypertension, the percentage reduction from the baseline in SBP (5.8%), DBP (5.9%)
and pulse pressure (5.7%) was all similar. This is in contrast with what has been
observed with thiazides and what was seen in the SHEP trial. In the SHEP trial,\cite{SHEP}
using chlorthalidone as first-line drug in patients with isolated systolic hypertension, the
percentage reduction from the baseline in SBP (7.6%) and pulse pressure (9.2%)
significantly exceeded the reduction in DBP (5.7%). In fact the SHEP trial results
expressed in this way closely correlates with the overall estimates seen in this review
SBP (6.3%), DBP (4.1%) and pulse pressure (9.7%). These observations may explain
why the benefits of calcium channel blockers on CHD events does not appear to be as
great for calcium-channel blockers as for thiazides and angiotensin converting enzyme
inhibitors.\cite{AngiotensinConvertingEnzymeInhibitors}
5. CLINICAL IMPLICATIONS

This systematic review has identified all the published research literature to date, related to the BP lowering of thiazide, thiazide-related and loop diuretics compared to placebo control in the treatment of hypertension. The findings of this review have important clinical implications.

1. The maximum doses of HCTZ that should be used to treat elevated BP is 25 mg/day and the average reduction in BP that can be achieved with that dose is 9/5 mm Hg.

2. The maximum doses of CTHD that should be used to treat elevated BP is 12.5 mg/day and the average reduction in BP that can be achieved with that dose is 10/3 mm Hg.

3. The maximum doses of IND that should be used to treat elevated BP is 1.0 mg/day and the average reduction in BP that can be achieved with that dose is 7/4 mm Hg.

4. The maximum dose of BDFZ that should be used to treat elevated BP is 1.25 mg/day and the average reduction in BP that can be achieved with that dose is 9/6 mm Hg.

5. The overall best estimate of blood pressure lowering efficacy of the highest dose of the defined low-dose range of thiazide diuretic monotherapy in primary hypertension for a mean duration of treatment of 9 weeks is 8.4/4.3 mm Hg.

6. Data for the BP lowering efficacy of loop diuretics are insufficient at present and it is not possible to say whether this is the same or different from thiazides.

7. Adverse metabolic effects are more common with doses higher than that needed to achieve a near maximal lowering of BP.
8. Low-dose, high-dose or overall combined doses of thiazide diuretic therapy have no significant effect on withdrawal due to adverse effects as compared to placebo in trials 3-12 weeks in duration in patients with primary hypertension.

9. The blood pressure lowering efficacy of low-dose thiazides is similar to high-dose thiazides with significantly less metabolic adverse effect; therefore, there is nothing to be gained by using high-doses of thiazide diuretics in the treatment of primary hypertension.

10. This systematic review has significant implications for the management of patients with elevated blood pressure. Dose titration to further lower BP in patients with elevated BP, beyond the maximum dose or dose range identified in this review for each drug within the thiazide and thiazide-related diuretics, is unjustified. If additional BP reduction is desired, a second drug from another first-line antihypertensive drug class should be added.
6. RESEARCH IMPLICATIONS

1. Despite over 4 decades of use of diuretics in hypertension, published data on the dose-response BP lowering efficacy of thiazide and loop diuretics are insufficient.

2. Because low-dose thiazide treatment shows BP lowering which approaches a maximum at doses which are at the lower end of those used clinically, more trials are needed at doses below this (HCTZ < 12.5 mg/day, CTHD < 12.5 mg/day and indapamide < 1.0 mg/day, CYPTZ < 125 μg/day, BDFZ < 1.25 mg/day and MTZ < 0.5 mg/day) to identify the lowest dose for each drug within the thiazide diuretic class.

3. Randomised placebo-controlled clinical trials are needed to establish dose-response BP lowering efficacy of other thiazides for which we found no randomised placebo controlled trials.

4. Head to head trial comparing doses with similar potency of HCTZ 12.5 to 25 mg/day and CTHD 6 to 25 mg/day should be done to definitively answer the question about the greater SBP lowering of CTHD as compared to HCTZ and IND.

5. Data relating to dose-response BP lowering efficacy of loop diuretics are severely lacking and the fact that loop diuretics have approval to treat patients with primary hypertension without this published evidence seems surprising.

6. More data are needed to better estimate many claims and counter-claims about withdrawal due to adverse drug effects and metabolic adverse effects of low- and high-dose diuretics.

7. Indexing of medical data bases is problematic and improving the existing deficiencies can improve searching of relevant articles to answer medically important questions.
8. The reporting of methodology in hypertension trials is problematic and standardised approaches giving adequate details about randomisation, allocation concealment and blinding should be required in all future trials.

9. The reporting in trials of baseline characteristics of patients in treatment as well as control group - age, race, existing co-morbidities or the other cardiovascular risk factors and the baseline SBP and DBP is extremely important in order to evaluate the effect size in the same trials and compare them between different trials.

10. The SBP and DBP level at baseline with SD, and most importantly the mean change from the baseline and SD of the change in both the treatment and the placebo groups should be reported in all trials. In trials were titration is allowed data should be reported at the end of monotherapy, before titrating to a higher dose or before additional drugs are added to control blood pressure. Actual numbers should be reported in the text or in a table and not presented as figures, because data abstraction from figures is difficult and inaccurate.

11. Withdrawal due to adverse drug effects, reasons for withdrawal and the time points at which patients withdrew needs to be reported in all trials.

12. Because lower doses have similar BP lowering efficacy as higher doses as shown in this systematic review, future long-term trials should use doses up to the doses defined as producing near maximal effects in this review.
7. REFERENCES


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