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The effect of indapamide versus bendroflumethiazide for primary hypertension: a systematic review

Short running title: Indapamide versus bendroflumethiazide

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Thiazide diuretics have long been demonstrated to be effective in lowering the risk of cardiovascular events by reducing blood pressure.
- In the UK, the thiazide bendroflumethiazide and the thiazide-like indapamide are the most prescribed diuretics for hypertension treatment.
- However, the comparative effectiveness of these two drugs is unclear.

WHAT THIS STUDY ADDS

- This review highlights a lack of studies on comparative efficacy of monotherapy with bendroflumethiazide versus indapamide on mortality, cardiovascular outcomes, blood pressure, need for intensification of treatment and treatment withdrawal.
- This review shows a lack of evidence of superiority of one drug over the other.
- There is a clear need for new studies directly comparing the effect of these drugs on the outcomes of interest.

Abstract

Aims

The aims were to compare the efficacy of monotherapy with bendroflumethiazide versus indapamide on mortality, cardiovascular outcomes, blood pressure, need for intensification of treatment and treatment withdrawal.

Methods

Two authors independently screened results of literature search, assessed the risk of bias and extracted relevant data. Randomized clinical trials of hypertensive patients of at least one-year duration were included. When there was disagreement, a third reviewer was consulted. Risk ratio (RR) and mean differences were used as measures of effect.

Results

Two trials comparing bendroflumethiazide against placebo, one comparing indapamide with placebo and three short duration trials directly comparing indapamide and bendroflumethiazide were included. No statistically significant difference was found between indapamide and bendroflumethiazide for all deaths (RR 0.82; 95% Confidence Interval (CI) 0.57-1.18), cardiovascular deaths (RR 0.82; 95%CI 0.55-1.20), non-cardiovascular deaths (0.81; 95%CI 0.54-1.22), coronary events (RR 0.73; 95%CI 0.30-1.79) or all cardiovascular events (RR 0.89; 95%CI 0.67-1.18). Indapamide performed worse for stroke (RR 2.21; 95%CI 1.19-4.11), even though a reduction in RR compared to placebo was observed in both groups. There was no statistically or clinically significant difference between indapamide and bendroflumethiazide in blood pressure reduction (mean absolute difference <1mmHg).

Conclusion

This review highlights a lack of studies to answer the review question but also a lack of evidence of superiority of one drug over the other. Therefore, there is a clear need for new studies directly comparing the effect of these drugs on the outcomes of interest.

Key words:

Systematic review; hypertension; bendroflumethiazide; indapamide; cardiovascular; mortality; thiazide diuretics;

Introduction

High blood pressure is one of the most important preventable causes of premature cardiovascular morbidity and mortality worldwide. World Health Organization (WHO) estimates the global prevalence in adults aged 25 years and over is around 40%. Raised blood pressure is estimated to cause 7.5 million deaths annually, about 12.8% of the total of all deaths. Moreover, hypertension increases the risk of developing coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, chronic kidney disease, cognitive decline and early death.[1] Treating hypertension reduces cardiovascular disease risk and the risk of death from cardiovascular causes.[2] Thiazide diuretics are a class of antihypertensive medications launched in the 1950s and have long demonstrated effectiveness in reducing blood pressure and the risk of cardiovascular events.[3] A recent Cochrane systematic review of first line drugs for hypertension concluded that *"low-dose thiazides should be the first-choice drug in most patients with elevated blood pressure"* due to the evidence of reduced mortality and morbidity such as stroke, heart attack and heart failure.[4] Usually prescribed as first-line or second-line drug, alone or combined with drugs from other classes, [5,6] diuretics are classified into thiazides and thiazide-like diuretics.[7] The most recent National Institute for Health and Clinical Excellence (NICE) guidelines for the management of *hypertension published in 2011* [8] *and evidence updated in 2013* [9] *specified that if "… a diuretic is required", "… a thiazide-like diuretic, such as chlortalidone (12.5 mg–25 mg once daily) or indapamide (2.5 mg once daily)" should be chosen … "in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorthiazide".* However, there has been debate around whether these guidelines were supported by evidence.[10] The existing systematic reviews

and meta-analyses focussed on efficacy of blood-pressure lowering [11,12,13,14,15] rather than long-term outcomes.[16,17,18]

The primary objective of the present review was to compare efficacy of monotherapy with the thiazide diuretic bendroflumethiazide versus the thiazide-like diuretic indapamide as first-line in the treatment of primary hypertension on mortality and cardiovascular outcomes. The secondary objective was to compare the effect of these two monotherapies on secondary outcomes such as blood pressure lowering, the need for intensification of treatment and medication discontinuation.

Methods

The protocol for this review was registered with the international prospective register of systematic reviews (PROSPERO)[19], registration number CRD42017067109. PRISMA guidelines [20] were followed for conducting and reporting of this review.

Literature search strategy

Literature search was performed from 2008 to April 2018 using the search strategy of Wright and Musini (2009) [4] and the NICE guidelines update 2013 [9] modified to focus on indapamide and bendroflumethiazide. MEDLINE, EMBASE, CINAHL (using NHS Education for Scotland The Knowledge Network), the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), Health Technology Assessment Database, ClinicalTrials.gov, EU Clinical Trials Register and Google Scholar were searched. In addition, two high-impact peer reviewed journals appropriate for this review, British Journal of Clinical Pharmacology and the European Heart Journal, were hand

searched for the past five years. References of the relevant published papers were also searched to help identify additional trials. Only publications in English language were included in this review.

Inclusion and exclusion criteria

Randomized controlled trials of adults with primary hypertension with at least one year follow up were included. Studies reporting monotherapy with bendroflumethiazide or indapamide were included where the comparator group was either a placebo or another drug. Supplemental medication with other drug classes were allowed as stepped-care therapy. It was assumed that these supplemental drugs did not systematically interact to affect the occurrence of the outcomes studied.

Data extraction

Two reviewers independently screened the title and the abstract of each study meeting the inclusion criteria. If disagreements occurred between the two reviewers, a third reviewer was consulted. For eligible studies, data extraction was performed by two reviewers independently using a specially designed data collection form. Disagreements were resolved after discussion with two other reviewers. The values of mean change from baseline in blood pressure at one year follow up and standard deviation were obtained from Wright and Musini (2009) [4] . Authors of studies were contacted, where the required information was clearly available but was not reported in the manuscript.

Outcomes

The primary outcomes considered were total mortality and cardiovascular outcomes such

as stroke, myocardial infarction, congestive heart failure and cardiovascular death. The secondary outcomes were adverse events, need for intensification of treatment, withdrawals and blood pressure lowering. Only published information was used in this review.

Risk of bias in the included studies

The Cochrane Collaboration's tool for assessing risk of bias [21] was used to assess quality in the included studies. Items of methodological quality assessed were: method used to randomize participants, whether randomization was completed in an appropriate and blinded manner; whether participants, providers, outcome assessors, or a combination of these were blinded to assigned therapy; whether the control group received a placebo or no treatment; percent of participants who did not complete follow-up (drop-outs); percent of participants not on assigned active or placebo therapy at study completion; selective reporting of outcomes. Two reviewers conducted the assessment independently. If disagreement occurred, a third reviewer was consulted. The results were compared with those reported by Musini et al.[22,23]

Data analysis

Network meta-analysis was conducted using STATA 15 for Windows (2017). All analysis were intention-to-treat. Indirect comparisons were made using *indirect* STATA command.[24] Graphical tools [25] were used as appropriate. Evidence was graded using approach of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [26] working group using GRADEpro.[27]

Results

Search results

The search resulted in 1878 publications (Figure 1). After the removal of duplicates and 1418 irrelevant papers and having found additional 26 papers from hand searching the references of published papers, 128 full text papers were considered further. Reasons for exclusion of 112 articles are shown in Figure 1. Reviews, meta-analyses, commentaries, editorial and protocols were published in 52 articles, while 60 articles contained information from 53 individual studies. The most common reason for study exclusion was duration of treatment (<1 year) (n=22) followed by combination therapy (n=13) and trials not being a trial of hypertension (n=12). Other excluded studies were observational studies (n= 3), single arm trials (n= 3), not studies of bendroflumethiazide or indapamide (n= 5) or studies where exposure was any thiazide diuretic (n= 4).

Three further studies (HYVET Pilot [28]; DIME[29] and HAPPHY [30]) were excluded because the participating centres within each study were given a choice of type of thiazide diuretics depending on drug availability, but the published manuscripts did not report the results by type of drug. When contacted, authors or funders either did not reply, could not provide the information required or could not make the original datasets available for data analysis. Therefore, three studies reported in seventeen papers were included in this review.[31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47]

Because no studies of a direct comparison between indapamide and bendroflumethiazide for long-term outcome were found, we included three studies of short term follow up with blood pressure as an outcome.[48,49,50]

Description of the included studies and study participants

Two studies were conducted in the United Kingdom [31,33] and one study was a multicentre clinical trial [42] (Table 1). They were published between 1973 and 2008. Study size ranged from 116 to 17,354 participants, and females comprised between 48% and 60%. Two studies included participants of mean age around 50-55 years, while in one study [42] the mean age of participants was 84 years. In two studies participants were followed up annually for 5 years [33,42] and one study followed the participants up to 18 months.[31]

All studies had pharmaceutical industry sponsorship. Participants were recruited from a variety of sources, such as surveys of random samples of general population, hospitals and primary care (Table 2). Mild, moderate and persistent hypertension was used as inclusion criteria, and there was variation in the method of blood pressure measurement (Table 2). Two studies investigated Bendroflumethiazide [31,33] and one study investigated indapamide [42](Table 3). All three trials used placebo as a comparison and one study also used propranolol.[33] Doses of all medications varied, and one study [31] did not specify the dose. All studies permitted additional medication at the discretion of physician or trial investigators (Table 3). Three short-term outcome studies directly comparing indapamide and bendroflumethiazide are described in Appendix 4. They were conducted in 1981 [48,49] and 2006 [50], each included less than 30 participants with follow up between 4 and 16 weeks.

Definition of outcome

Table 4 shows the availability of data on primary and secondary outcomes. Two trials [33,42] had all primary outcomes data available, while the cause of death was missing for

two participants in the placebo group in Barraclough et al.[31] All studies reported withdrawals for medical reasons, however the reported reasons differed between studies. For example, Barraclough et al [31] participants in the placebo group with diastolic blood pressure >130mmHg were withdrawn by design. There were insufficient data for other secondary outcomes such as additional medication, while data on diastolic blood pressure were reported in all studies and information on systolic blood pressure was available in two studies.[33,42]

Risk of bias in the included studies

Table 5 shows results of the assessment of risk of bias in each of the included studies. Two studies[31,33] did not satisfy criteria for blinding and data completeness, two studies were not free of selective reporting[31,42] one trial had inadequate allocation concealment and in one study[42] random sequence generation was unclear. Appendix 5 shows results of the assessment of risk of bias in each of the three short-term outcome studies directly comparing indapamide and bendroflumethiazide. All three studies had high risk of bias.

Effects of interventions

Appendix 1 shows the data extracted for each outcome and effect of intervention for each study compared to placebo. In addition, Appendix 2 shows a forest plot by outcome for each study. Appendix 3 illustrates the network pattern, and Appendix 1 presents results of the indirect comparison of indapamide versus bendroflumethiazide. There was no statistically significant difference between indapamide and bendroflumethiazide on all deaths (indirect RR 0.82; 95% CI 0.57, 1.18), cardiovascular death (indirect RR 0.82; 95% CI 0.55, 1.20), non-cardiovascular death (indirect RR 0.81; 95% CI 0.54, 1.22), coronary events (indirect RR 0.73; 95% CI 0.30, 1.79) or all cardiovascular events (indirect RR

0.89; 95% CI 0.67, 1.18). However, whilst indapamide showed a reduction in risk for these outcomes compared to placebo, bendroflumethiazide did not show a difference compared to placebo for these outcomes except for all cardiovascular events combined (Appendix 1, 2). Indapamide performed worse for the outcome of stroke and withdrawals for medical reasons (indirect RR 2.21; 95% CI 1.19, 4.11 and RR 1.23; 95% CI 1.07, 1.40, respectively). However, there was a reduction in RR compared to placebo in both of these groups except for withdrawals for medical reasons in the indapamide group (RR 0.98; 95% CI 0.89, 1.07) (Appendix 1,2).

Significant long-term reductions in blood pressure from baseline, in comparison to placebo, were reported in all studies. There were no statistically or clinically significant difference between indapamide and bendroflumethiazide (mean difference in reduction from baseline 0.94; 95% CI -1.45, 2.25 and 0.88 95% CI -0.19, 1.95 mmHg) in systolic and diastolic blood pressure respectively (Appendix 1,2). Appendix 6 shows data extracted for systolic and diastolic blood pressure for each study of the direct comparison between indapamide and bendroflumethiazide, while Appendix 7 shows a forest plot and summary effects. There was no statistically or clinically significant difference between indapamide and bendroflumethiazide (mean difference -0.26; 95% CI -0.79, 0.27 and -0.40 95% CI --0.93, 0.14 mmHg) for systolic and diastolic blood pressure respectively (Appendix 7).

There were only three studies included in meta-analysis of long-term outcomes and three studies of short-term blood pressure reduction. Appendix 8 shows funnel plots for these studies. There did not appear to be any evidence of publication bias for short term

outcomes as the figure for both types of blood pressure were symmetrical. However, this was less clear in case of indirect comparisons.

Overall evidence

Evidence was graded either as moderate or low (Tables 6 and 7).

Discussion

Bendroflumethiazide and indapamide are the most frequently prescribed diuretics for hypertension treatment in the UK.[51] This is the first systematic review to directly compare indapamide and bendroflumethiazide. It demonstrates the lack of evidence on comparative effectiveness of these drugs on mortality and cardiovascular outcomes such as stroke and myocardial infarction, as only three eligible studies were available for analysis of these long-term outcomes, and none were studies of direct comparison. Three small studies of direct comparison were prone to bias, with low overall GRADE evidence. A meta-analysis of thiazide-like diuretics versus thiazide-type diuretics which included twelve studies comparing indapamide or chlorthalidone versus hydrochlorothiazide suggested that thiazide-like diuretics further reduce both systolic and diastolic BP (mean -5.59 mmHg 95% CI -5.69, -5.49 and -1.98 95% CI -3.29, -0.66, respectively.[52]

A network meta-analyses that aimed to summarise the evidence on efficacy of antihypertensive therapies[53] included 42 clinical trials randomised to seven types of treatment. Treatments considered were placebo, untreated, or usual care: low-dose diuretics; β-blockers; angiotensin-converting-enzyme (ACE) inhibitors; Angiotensin II receptor blockers (ARBs); Calcium channel blockers (CCBs); and α-blockers. This meta-analysis showed that low-dose diuretics were the most effective first-line treatment for

preventing the occurrence of cardiovascular disease morbidity and mortality compared to other treatments. However, the low-dose diuretic therapies were usually the equivalent of 12.5 to 25 mg per day of chlorthalidone or hydrochlorothiazide.

Whilst only a limited number of studies were included in the present review, its strengths included having a pre-defined protocol and it followed current guidelines and statistical techniques. Every effort was made to find relevant studies, and multiple sources were searched. The search strategy was similar to those strategies used in previous systematic review [4] and clinical guidelines update.[9] To minimise potential errors, the selection of studies and data extraction were performed independently by two reviewers and was also compared to data extracted in other systematic reviews.[22,23]

Nevertheless, there are many methodological limitations. We restricted our search to publications in English language, which could potentially influence the results. However other countries use mostly other types of thiazides such as chlorthalidone, metolazone or hydrochlorothiazide.[54,55,56,57,58] Whilst one study[42] was international, other studies included in this review were conducted only in the UK.[31,33]

We have formally evaluated publication bias, but the number of studies included in this review was small. It is possible that some studies, especially earlier studies, were never published. We searched clinical trials registers as well as data bases of published literature but did not find any more. Although three studies eligible for inclusion had the required data available, we could not get access to the original data and therefore could not include them in this review.

There was substantial heterogeneity between the studies included in this review. Firstly, hypertension was defined differently between the studies. For example, Hyvet study[42]

considered systolic BP while the other studies[31,33] considered diastolic BP.

Studies measured BP differently, i.e. supine, sitting or standing, and clinic or monitoring at home; or one-off measurement or average of measurements from several occasions.

Inclusion criteria were different between studies. In the HYVET study[42] patients were previously treated for hypertension but suspended their treatment for at least 2 months prior to entry to the study while in the other two trials[31,33] the enrolled participants didn't take any medication for hypertension prior to enrollment.

Participants were recruited from various sources such as general population, medical practices and hospitals; therefore, it is difficult to judge the overall generalizability of the findings.

One study[31] had follow up of 18 months, while two other studies were long-term follow up (over 5 years). However, the results were also available for 2 years follow up in the HYVET study [42] and 5.5 years follow up in MRC-TH study.[33] In addition, it was possible to estimate blood pressure results for one year follow up from graphs in all three studies.

Dose information was not available in one study.[31]

Another potential limitation is the fact that some of the trials included a thiazide combined

with another drug. For example, in the Hyvet study,[42] at 2 years follow-up, 73.4% of the active group received both indapamide and perindopril.

Outcome data were not always complete or were heterogeneous. For example, cause of death was missing for some participants in Barraclough.[31] This study also withdrew controls with diastolic BP>130mmHg but not the active group. There were different reasons for medical withdrawals between studies as well as inconsistent reports of non-medical withdrawals between studies. Additional medication was insufficiently reported to allow meaningful data analysis. One study [31] did not report data on systolic BP. Data for some parameters, such as standard deviation, were not always available, especially in the earlier studies, and therefore assumptions were made using baseline estimates or estimates from other studies. This could potentially introduce bias to the overall estimates.

Quality of the included studies varied, for example one long-term trial [42] and one short-term trails[50] were double-blind. Two studies were large[33,42] while the study by Barraclaugh[31] and three studies of direct comparison were rather small (less than 30).

All long-term studies and one short-term study reported some form of pharmaceutical industry support. However, while the importance of knowledge of who funded a study is widely agreed, it was argued that Cochrane risk of bias tool should not include funding source as a standard item.[59] Conflict of interest in industry-funded trials are likely to manifest in selective reporting or problematic choice of comparator. To counteract the former, we searched trial registers and, where possible, accessed study protocols. To counteract the latter, it was suggested that network meta-analysis can be used for head-to-head drug comparisons where placebo comparators were used [59], which was used in this review.

There are several potential methodological problems associated with indirect comparison.[60] While the combined sample size of the included studies was large, the number of studies available for this review was small. Methods for estimating the effective number of trials and effective sample size were proposed, which take into account trial count ratio. For trial count ratio 1:2 (for example in this review there were two studies of bendroflumethiazide and one study of indapamide), the indirect comparison would require 6 trials (ratio 2:4) to produce precision equivalent to one head-to head trial.[61]

We did not combine indirect and direct evidence as the direct evidence came from small short-term trials reporting blood pressure only, while the primary aim of this study was to compare long-term cardiovascular outcomes. However, it is reassuring that both direct and indirect estimates of effect of the drugs on blood pressure were similar. In addition, reduced blood pressure seemed to stabilise after one year follow up.[33,42]

We compared bendroflumethiazide and indapamide indirectly via placebo. Placebo composition was stated only in one trial[31] while other studies stated that placebo was essentially a look-alike of the active treatment. While there were studies of direct comparison of hydrochlorothiazide versus indapamide and hydrochlorothiazide versus placebo[4,52], they were not included because these drugs are rarely used in the UK.[51]

One of the requirements of indirect meta-analysis is that the population groups are comparable. Two studies in this review involved participants below age 80 years [31,33] while one study[42] was conducted in patients aged over 80 years. One might argue that these groups are incomparable. Is there any evidence of differential action of these drugs in different age groups? A systematic review of pharmacotherapy for hypertension in adults aged 18 to 59 years[15] includes seven studies and 17,327 participants, and the MRC TH

trial[33] which is also included in the current review constituted 84% of the population considered. The review demonstrated a small absolute effect to reduce cardiovascular mortality and morbidity, no reduction in all-cause mortality and coronary and lack of good evidence on withdrawal due to adverse events.

On the other hand, a systematic review of pharmacotherapy for hypertension in the elderly [23] included fifteen trials and 24,055 participants of age 60 and over with moderate to severe hypertension. The review showed a reduction in all-cause mortality and cardiovascular morbidity and mortality, but the decrease in all-cause mortality was limited to persons aged 60 to 80 years. The process of grading the evidence is subjective, and the issue of grade inflation has been highlighted previously.[62] In this review evidence was graded either as low or moderate, and grading was done by authors' consensus, to minimise potential overestimation.

Guidance for policy makers in interpreting indirect treatment comparisons and network meta-analysis is available,[63,64] however our results are unlikely to be used for clinical decision-making due to deficiency of evidence.

In this systematic review, we have determined, from small number of studies, that the information on direct comparison between indapamide and bendroflumethiazide is very limited and the evidence of superiority of indapamide over bendroflumethiazide on long term outcomes is inconclusive. Therefore, there is a clear need for large clinical trials directly comparing these two drugs. In fact, there are two ongoing studies. The BISON (bendroflumethiazide versus indapamide for primary hypertension: observational) study within Clinical Practice Research Datalink (CPRD)[65] is designed to compare the effect of bendroflumethiazide versus indapamide on risk of cardiovascular outcomes using real

world data. The EVIDENCE (Evaluating Diuretics in Normal Care) study is a cluster randomised evaluation of hypertension prescribing policy in which GP surgeries have their practice drug formularies randomised to either indapamide or Bendroflumethiazide.[66]

In summary, we have no good comparative effectiveness data on the two most commonly prescribed diuretics for hypertension in the UK.

Acknowledgements

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Figure 1. Flow Diagram

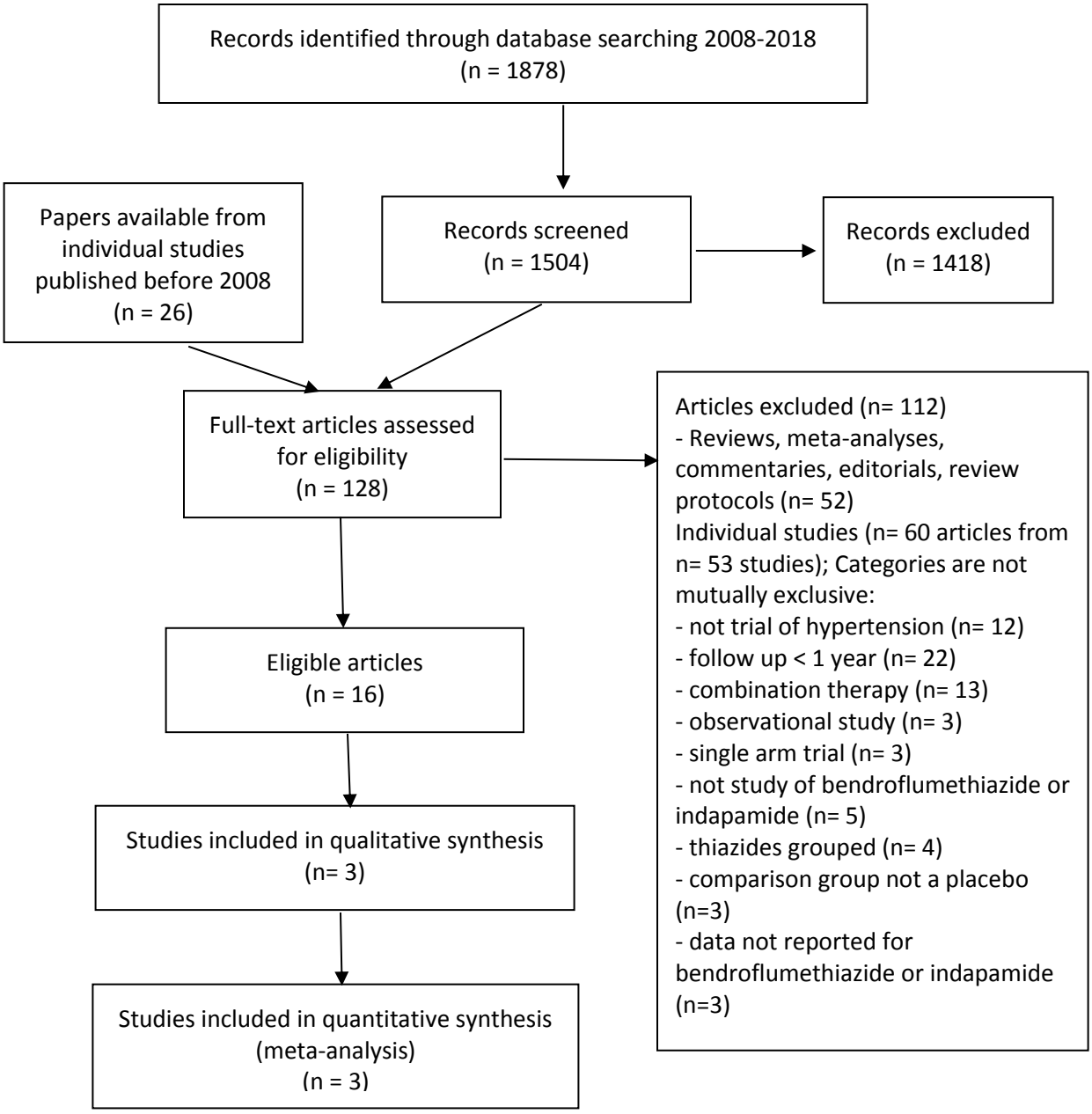


Table 1. Description of the included studies and study participants

First author/ Publication year/ Study name	Country	Study size	Follow up #	Age (years)	Sex N (%) females	Sponsorship
Barraclough 1973 Co-operative Randomised Controlled Trial	UK	116	6, 12, 18 months	Mean Treatment group: Men 54.4 Women 55.7 Placebo: Men 55.2 Women 56.5 Range 45-69	66 (57%)	Drugs were supplied by Glaxo Ltd., Merck Sharp and Dohme Ltd., and Roche Products Ltd.
MRC working party 1985 MRC-TMH	UK	17,354	1, 2, 3, 4, 5 years	Mean Males: 51 (SD 8) Females: 53 (SD 7)	8,306 (48%)	Drugs were supplied by Duncan, Flockhart and Co Ltd, Imperial Chemical Industries Ltd, CIBA Laboratories and Merck Sharp & Dohme Ltd Additional support was also provided by Imperial Chemical Industries Ltd and Merck Sharp and Dohme Ltd.
Beckett 2008 HYVET	UK, France, Ireland, Finland, Belgium, Bulgaria, Romania, Poland, Russia, China, Australia, New Zealand, Tunisia	3,845	1, 2, 3, 4, 5 years	Mean 84 (SD 3) Range 80-105	2,326 (60%)	Supported by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier

Follow up time when outcomes of interest were available

Table 2. Description of studies by inclusion and exclusion criteria

First author/ Publication years/ Study name	Population	Definition of hypertension	How baseline blood pressure was measured	Age inclusion criteria (years)	Exclusion criteria
Barraclough 1973 Co-operative Randomised Controlled Trial	Surveys of random samples of general population and hospital patients	Diastolic BP 100-120 mm Hg Two occasions separated by an interval of at least 2 weeks	Garrow random-zero sphygmomanometer after sitting for 5 min.	45-69	Renal or cardiac failure or papilloedema; history of cerebrovascular accident or MI within the past 3 months; any serious or potentially fatal disease or disability that would prevent regular attendances or which contraindicated hypotensive therapy; receiving antihypertensive therapy; evidence that hypertension was secondary to a surgically remediable condition.
MRC working party 1985 MRC-TMH	General medical practice clinics	Diastolic pressure 90-109 mm Hg and systolic pressure < 200 mm Hg; Mean of 4 readings taken on 2 separate occasions and confirmed by the mean of 2 later readings	Hawksley random zero sphygmomanometer and London School of Hygiene sphygmomanometer	35-64	Secondary hypertension; taking antihypertensive treatment; normally accepted indications for antihypertensive treatment (such as congestive cardiac failure present); MI or stroke within the previous 3 months; presence of angina, intermittent claudication, diabetes, gout, bronchial asthma, serious intercurrent disease, or pregnancy
Beckett 2008 HYVET	Patients	Sustained systolic BP ≥160 mm Hg during 2 months of placebo run-in period; BP taken twice after sitting for 5 min and on the third visit and thereafter twice after standing for 2 min; Mean of 2 sitting SBP readings taken on 2 separate occasions, 1 month apart, between 160 and 199 mmHg Standing SBP≥140 mmHg	Standard mercury sphygmomanometer or validated automatic device.	≥80	Known accelerated hypertension, heart failure requiring treatment with diuretic or ACE inhibitor, renal failure (serum creatinine level > 150 μmol/L), haemorrhagic stroke in the previous 6 months, terminal illness, known secondary hypertension, gout, clinical diagnosis of dementia, contraindication to use of the trial medications (a serum potassium level of < 3.5 mmol/L or > 5.5 mmol/L) and a requirement of nursing care, inability to stand up or walk

BP Blood pressure; MI myocardial infarction

Table 3. Description of interventions

First author, Publication year	Indapamide	Bendroflumethiazide	Placebo	Propanolol	Additional treatment
Barraclough 1973 Co-operative Randomised Controlled Trial	-	Dose is not specified	Calcium lactate	-	Bendrofluazide group: any combination with potassium supplement, methyldopa, or debrisoquine (discretion of physician)
MRC working party 1985 MRC-TMH	-	10 mg daily	Tablets that looked like bendrofluazide or tablets that looked like propranolol	240 mg daily	Methyldopa or guanethidine was added if blood pressure did not respond satisfactorily to the primary drug. If necessary, one of the primary trial drugs was used to supplement the other. Control patients whose blood pressure rose to levels at which placebo treatment was judged unethical were transferred to the corresponding active drug. For BP >110 mm Hg diastolic and > 200 mm Hg systolic in active treatment group additional treatment used on discretion of physician.
Beckett 2008 HYVET	1.5 mg SR daily	-	Matching placebo	-	At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added

Table 4. Availability of data on outcomes

Outcome	First author/ Publication year/ Study name		
	Barraclough 1973; Co-operative Randomised Controlled Trial	**MRC working party 1985; MRC-TMH**	**Beckett 2008; HYVET**
Timing of outcome	18 months	Mean 5.5 years	Median follow up 1.8 years
All deaths	Yes	Yes	Yes
Cardiovascular deaths	Yes (cause of death was unknown for some of the participants)	Yes	Yes (Death from fatal stroke, fatal myocardial infarction, fatal heart failure and sudden death)
Non-cardiovascular deaths	Yes (cause of death was unknown for some of the participants)	Yes	Yes
Stroke	Not reported (Assumed 0)	Yes (fatal or non-fatal)	Yes (fatal or nonfatal)
Myocardial infarction	Yes (fatal or nonfatal)	Yes (Coronary events including sudden death thought to be due to a coronary cause, death known to be due to myocardial infarction, and non-fatal myocardial infarction)	Yes (fatal or nonfatal)
Other cardiovascular events	Yes (Pulmonary embolism; Cardiac failure)	Yes (Other cardiovascular events, including deaths due to hypertension (ICD 400-404) and to rupture or dissection of an aortic aneurysm; death from any other cause)	Yes
Any cardiovascular events	Yes	Yes (Not necessarily equal to the total of strokes plus coronary events because it also includes “other relevant deaths” and death due to other cardiovascular causes such as ruptured aneurysms)	Yes (Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure)
Withdrawals for medical reasons #	Yes (Participants from the control group with diastolic BP>130mmHg were withdrawn by design; geriatric hospital admission in the bendroflumethiazide group)	Yes (Impaired glucose tolerance; Gout; Impotence, Raynaud’s phenomenon; Skin disorder; Dyspnoea; Lethargy; Nausea, dizziness, headache; BP at levels requiring change of treatment)	Yes (Were withdrawn by investigator; Had a protocol withdrawal event and no open follow-up)
Withdrawals for non-medical reasons	Yes (Defaulted or non-cooperative)	No	Yes (centres closed by data monitoring committee; had other administrative reasons; declined to participate; lost to follow-up)
Additional medication	No additional medication in control group by design; All participants in the active group had additional medication	Not reported for placebo	Yes
Blood pressure	Yes	Yes	Yes

not including primary outcomes;

Table 5. Assessment of risk of bias

First author/ Publication year/ Study name	**Random sequence generation**	**Allocation concealment**	***Blinding of participants and personnel***	**Blinding of outcome assessment**	**Incomplete outcome data**	**Free from selective reporting**	**Other sources of bias**
Barraclough 1973 Co-operative Randomised Controlled Trial	+	-	-	+	-	-	?
MRC working party 1985 MRC-TMH	+	+	-	+	-	+	?
Beckett 2008 HYVET	?	+	+	+	+	-	?

Table 6. Grading the evidence: primary outcomes

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide	Bendro-flumethiazide	Relative (95% CI)		
All deaths (follow up: range 1.5 – 5.5 years)											
3	randomised trials	not serious	not serious	very serious	not serious	none	1933	4355	RR 0.82 (0.57 to 1.18)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular deaths (follow up: range 2-5.5 years)											
2	randomised trials	not serious	not serious	very serious	not serious	none	1933	4297	RR 0.82 (0.56 to 1.20)	⊕⊕◯◯ LOW	CRITICAL
Non-cardiovascular deaths (follow up: range 2-5.5 years)											
2	randomised trials	not serious	not serious	very serious	not serious	none	1933	4297	RR 0.81 (0.54 to 1.22)	⊕⊕◯◯ LOW	CRITICAL
Stroke (follow up: range 2-5.5 years)											
2	randomised trials	not serious	not serious	very serious	not serious	none	1933	4297	RR 2.21 (1.19 to 4.11)	⊕⊕◯◯ LOW	CRITICAL
Coronary events (follow up: range 1.5-5.5 years)											
3	randomised trials	not serious	not serious	very serious	not serious	none	1933	4355	RR 0.73 (0.30 to 1.79)	⊕⊕◯◯ LOW	CRITICAL
All cardiovascular events (follow up: range 2-5.5 years)											
2	randomised trials	not serious	not serious	very serious	not serious	none	1933	4297	RR 0.89 (0.67 to 1.18)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Table 7. Grading the evidence: secondary outcomes

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide	Bendro-flumethiazide	Absolute (95% CI)		
Systolic blood pressure mmHg (follow up: 1 year)											
2	randomised trials	not serious	not serious	serious	not serious	none	1933	4297	0.94 (-1.45, 2.25)	⊕⊕⊕◯ MODERATE	CRITICAL
Diastolic blood pressure mmHg (follow up: 1 year)											
3	randomised trials	not serious	not serious	serious	not serious	none	1933	4355	0.88 (-0.19, 1.95)	⊕⊕⊕◯ MODERATE	CRITICAL
Systolic blood pressure mmHg (follow up: range 12 - 24 weeks)											
3	randomised trials	serious	not serious	not serious	serious	none	29	27	-0.26 (-0.79, 0.27)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic blood pressure mmHg (follow up: range 12 - 24 weeks)											
3	randomised trials	serious	not serious	not serious	serious	none	29	27	-0.40 (-0.93, 0.14)	⊕⊕◯◯ LOW	IMPORTANT

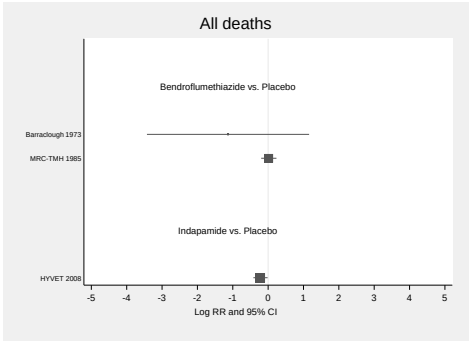
CI: Confidence interval

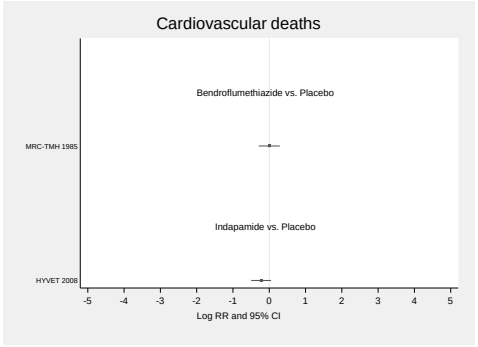
Appendix 1. Results by type of outcome

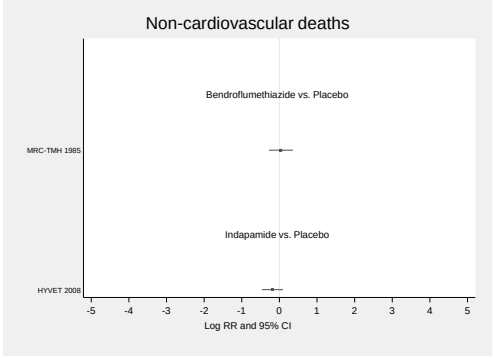
Number of events by type of outcome	Barraclough 1973 Co-operative Randomised Controlled Trial			MRC working party 1985 MRC-TMH			Beckett 2008 HYVET			Indirect comparison indapamide vs bendroflumethiazide
Treatment group	Bendro-flumethiazide N=58	Placebo N=58	RR (95% CI) *	Bendro-flumethiazide N=4,297	Placebo N=8,654	RR (95% CI) *	Indapamide N=1,933	Placebo N=1,912	RR (95% CI) *	RR (95% CI) *
All deaths	1	3	0.33 (0.04, 3.11)	128	253	1.02 (0.82, 1.26)	196	235	0.82 (0.69, 0.99)	0.82 (0.57, 1.18)
Cardiovascular deaths	-	-	-	69	139	0.99 (0.75, 1.33)	99	121	0.81 (0.63, 1.05)	0.82 (0.56, 1.20)
Non-cardiovascular deaths	-	-	-	59	114	1.04 (0.76, 1.42)	97	114	0.84 (0.65, 1.10)	0.81 (0.54, 1.22)
Stroke	0	0	-	18	109	0.33 (0.20, 0.55)	51	69	0.73 (0.51, 1.04)	2.21 (1.19, 4.11)
Coronary events	1	2	0.5 (0.05, 5.36)	119	234	1.02 (0.82, 1.27)	9	12	0.74 (0.31, 1.76)	0.73 (0.30, 1.79)
All cardiovascular events	-	-	-	140	352	0.80 (0.66, 0.97)	138	193	0.71 (0.57, 0.87)	0.89 (0.67, 1.18)
Withdrawals for medical reasons	1	9	0.11 (0.01, 0.85)	481	1215	0.80 (0.72, 0.88)	4	5	0.79 (0.21, 2.94)	-
Withdrawals for non-medical reasons	10	9	1.11 (0.49, 2.53)	0	0	-	647	656	0.98 (0.89, 1.07)	-
Systolic blood pressure mmHg * **	-	-	-	-25.2 (16.1) **	-13 (17.9)**	-12.20 (-13.00, -11.40) #	-25.7 (16.5)**	-13.9 (18.9)**	-11.80 (-13.47, -10.13) #	0.94 (-1.45, 2.25) #
Diastolic blood pressure mmHg * **	-20 (9.9)**	-5 (12)**	-15.00 (-21.61, -8.39)#	-12 (9.9)**	-6 (12)**	-6.00 (-6.51, -5.49)#	-11.8 (10.3)**	-6.6 (10.9)**	-5.20 (-6.20, -4.20)#	0.88 (-0.19, 1.95) #

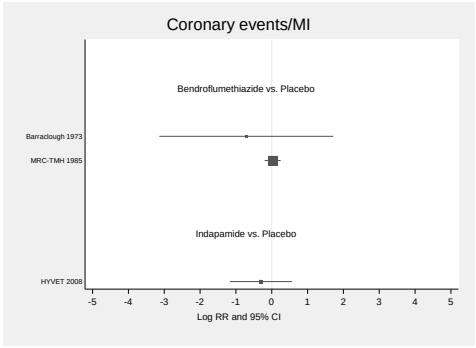
* unless otherwise specified ** Mean (SD) # Mean difference (95% CI) *** Change from baseline

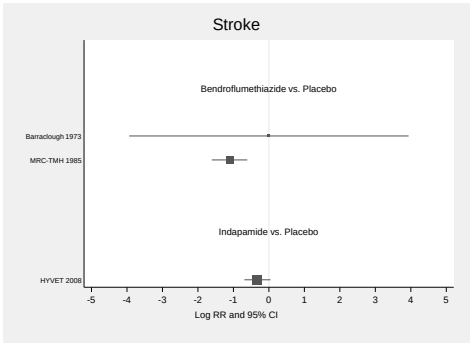
Appendix 2. Forest plots for long term outcomes

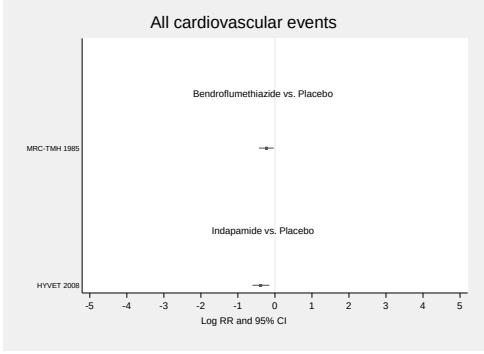


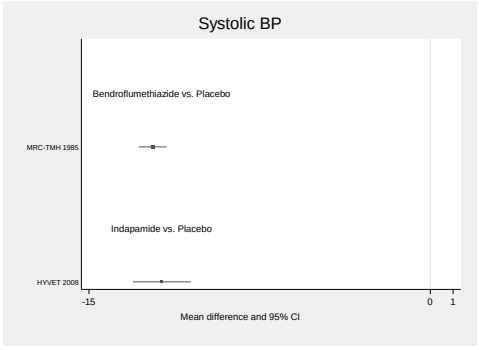


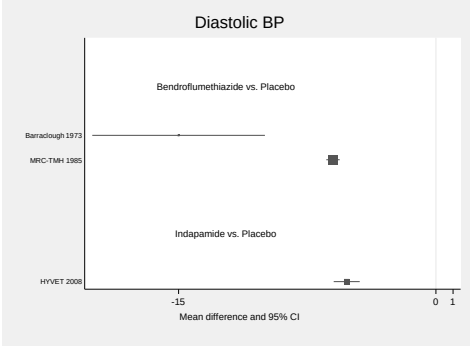




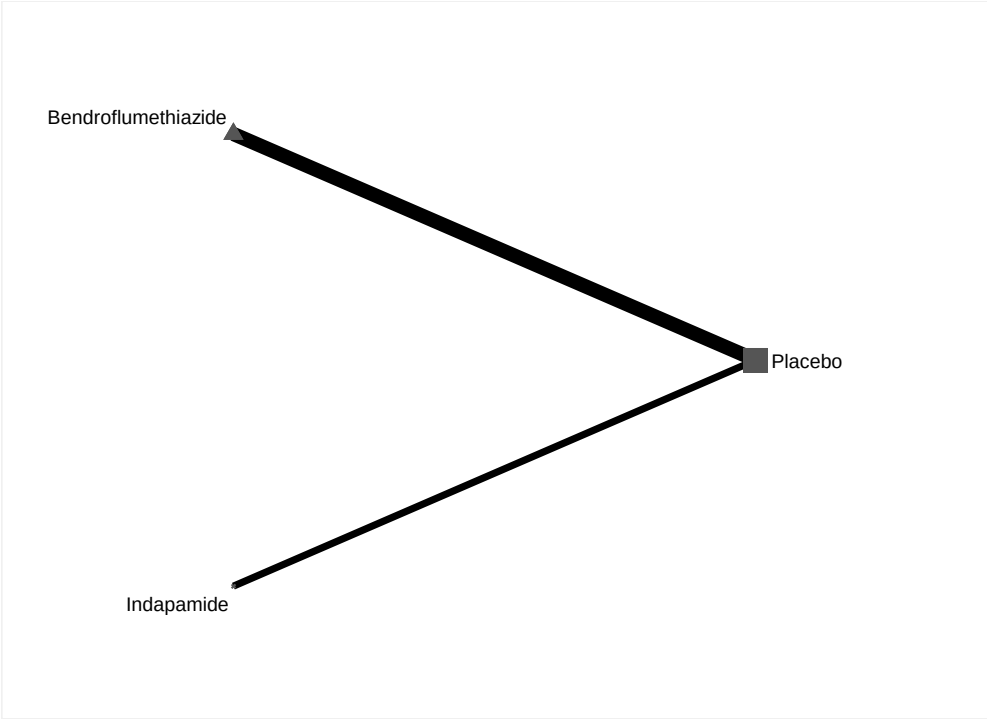








Appendix 3. Network pattern



Appendix 4. Description of studies of direct comparison between indapamide and bendroflumethiazie (short term outcome)

Study characteristic	First author/ Publication year/ #		
	Bing 1981	**Zacharias 1981**	**Milia 2006**
Population #	Hospital (Hypertension Clinic)	No information	Cerebrovascular clinic
Inclusion criteria	Mild essential hypertension (defined as diastolic BP ≥95mmHg)	Patients treated with atenolol 100 or 200 mg/day as their sole anti-hypertensive therapy for at least 8 weeks	Ambulant patients with first-ever minor hemispheric ischemic stroke or transient ischaemic attack (TIA) with or without hypertension status
Exclusion criteria	Clinical gout, abnormal renal function (judged by blood urea and serum creatinine)	Cardiac, renal or hepatic failure, known sensitivity to thiazide diuretics or pregnant	Significant post stroke disability (Barthel score <70), comorbidity or contraindication to antihypertensive treatment; pre-existing moderate to severe renal impairment (serum creatinine >200 mmol/L) or with ≥50% stenosis of either carotid artery, BP > 180/100 mmHg
Definition of hypertension	Mild essential hypertension (DBP ≥95 mmHg)	Hypertension not adequately controlled on atenolol alone	No information
How BP was measured	Ascultatory method; supine and upright position	Hawksley Random Zero Sphygmomanometer; supine and upright position	Critikon Dinamap equipment (mean of 3 measurements); supine position
Sponsorship	Servier Laboratories	No information	No information
Follow up	16 weeks on single drug, followed by 16 weeks of combined therapy (indapamide+bendroflumethiazide)	12 weeks	28 days
Age (years)	32-64	No information	68.8 ±10.6
Sex N (%) females	10 (50)	9 (53)	13 (50)
Indapamide	2.5 mg daily	2.5 mg + placebo-bendroflumethiazide 5 mg	2.5 mg daily
Bendroflumethiazide	5.0 mg daily	5 mg + placebo-indapamide 2.5 mg	2.5 mg daily
Study size Indapamide Bendroflumethiazide	20 10 10	17 No information No information	26 13 13

All studies were conducted in the UK

Appendix 5. Assessment of risk of bias

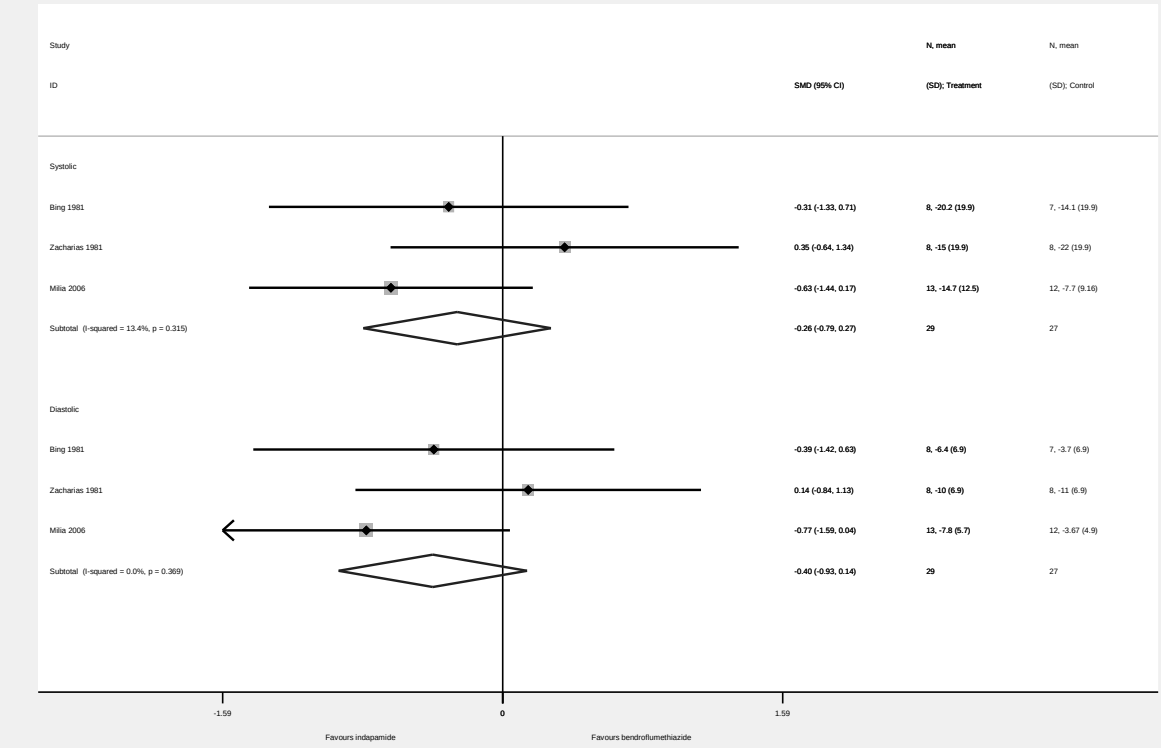
First author/ Publication year	***Random sequence generation***	***Allocation concealment***	**Blinding of participants and personnel**	***Blinding of outcome assessment***	***Incomplete outcome data***	***Free from selective reporting***	***Other sources of bias***
Bing 1981	-	-	-	-	-	-	?
Zacharias 1981	-	+	-	-	-	-	?
Milia P 2006	-	-	+	-	-	-	?

Appendix 6. Results for short-term blood pressure (studies of direct comparison)

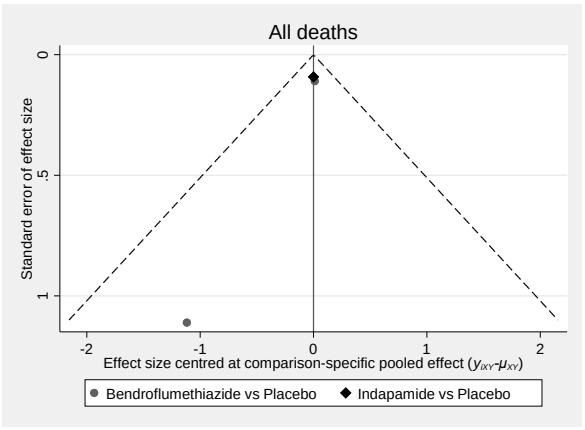
Study characteristic	First author/ Publication year/ #		
	Bing 1981 16 weeks follow up	**Zacharias 1981** 12 weeks follow up	**Milia 2006**
Group size (per protocol) Indapamide Bendroflumethiazide	 8 7	 Assumed 8 Assumed 8	 13 12
Withdrawals for medical reasons Indapamide Bendroflumethiazide	 1 (dizziness) 3 (1 dizziness; 2 uncontrolled hypertension)	 1 (at 20 weeks due to depression) 0	 0 1 (viral illness)
Withdrawals for non-medical reasons Indapamide Bendroflumethiazide	 1 (failed to complete the study) 0	 0 0	 0 0
Systolic blood pressure, supine (mmHg) *Indapamide* Baseline Mean (SD) Mean change from baseline (SD) *Bendroflumethiazide* Baseline Mean (SD) Mean change from baseline (SD)	 No information -20.2 (19.9) No information -14.1 (19.9)	 172 -15 * 181 -22 *	 145 (15.5) -14.7 (12.5) 134.8 (19.3) -7.7 (9.16)
Diastolic blood pressure, supine (mmHg) *Indapamide* Baseline Mean (SD) Mean change from baseline (SD) *Bendroflumethiazide* Baseline Mean (SD) Mean change from baseline (SD)	 No information -6.4 (6.9) * No information -3.7 (6.9) *	 101 -10 104 -11	 78.3 (7.4) -7.8 (5.7) * 73.4 (10.4) -3.67 (4.9) *
Author's conclusion	Indapamide produced a significant but equivalent fall in blood pressure to that observed with bendroflumethiazide	Both drugs produced a similar modest improvement in blood pressure	Both diuretics reduced blood pressure to a similar and significant degree

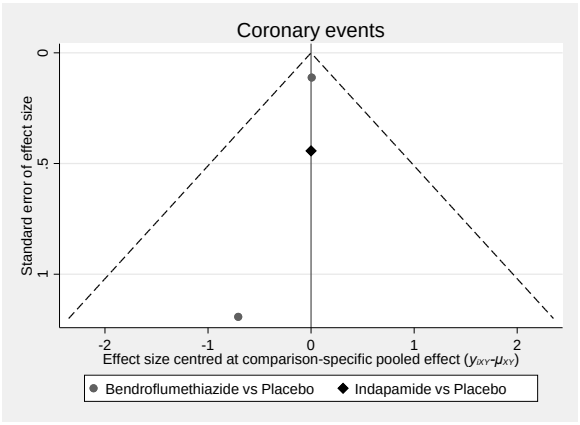
* Estimated from information in the paper

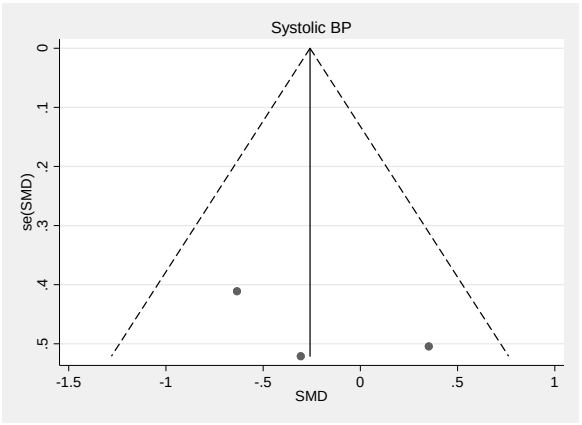
Appendix 7. Forest plot (short term outcome, studies of direct comparison)

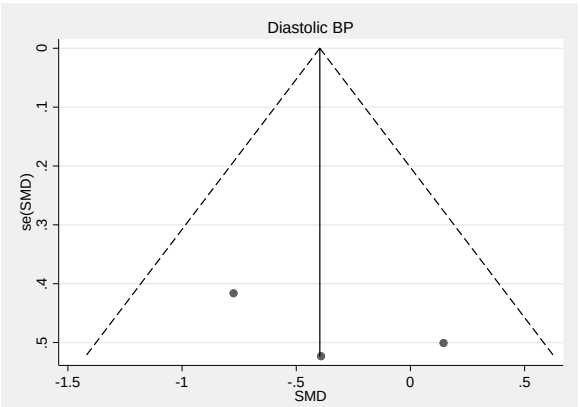


Appendix 8. Funnel plots for long-term outcomes (all deaths and coronary events) and short-term outcomes (blood pressure)









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