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First-line diuretics versus other classes of antihypertensive drugs for hypertension (Review)

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[Intervention Review]

First-line diuretics versus other classes of antihypertensive drugs for hypertension

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ABSTRACT

Background

Different first-line drug classes for patients with hypertension are often assumed to have similar effectiveness with respect to reducing mortality and morbidity outcomes, and lowering blood pressure. First-line low-dose thiazide diuretics have been previously shown to have the best mortality and morbidity evidence when compared with placebo or no treatment. Head-to-head comparisons of thiazides with other blood pressure-lowering drug classes would demonstrate whether there are important differences.

Objectives

To compare the effects of first-line diuretic drugs with other individual first-line classes of antihypertensive drugs on mortality, morbidity, and withdrawals due to adverse effects in patients with hypertension. Secondary objectives included assessments of the need for added drugs, drug switching, and blood pressure-lowering.

Search methods

Cochrane Hypertension's Information Specialist searched the Cochrane Hypertension Specialized Register, CENTRAL, MEDLINE, Embase, and trials registers to March 2021. We also checked references and contacted study authors to identify additional studies. A top-up search of the Specialized Register was carried out in June 2022.

Selection criteria

Randomized active comparator trials of at least one year's duration were included. Trials had a clearly defined intervention arm of a first-line diuretic (thiazide, thiazide-like, or loop diuretic) compared to another first-line drug class: beta-blockers, calcium channel blockers, alpha adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, direct renin inhibitors, or other antihypertensive drug classes. Studies had to include clearly defined mortality and morbidity outcomes (serious adverse events, total cardiovascular events, stroke, coronary heart disease (CHD), congestive heart failure, and withdrawals due to adverse effects).

Data collection and analysis

We used standard Cochrane methodological procedures.

Main results

We included 20 trials with 26 comparator arms randomizing over 90,000 participants. The findings are relevant to first-line use of drug classes in older male and female hypertensive patients (aged 50 to 75) with multiple co-morbidities, including type 2 diabetes. First-line thiazide and thiazide-like diuretics were compared with beta-blockers (six trials), calcium channel blockers (eight trials), ACE inhibitors (five trials), and alpha-adrenergic blockers (three trials); other comparators included angiotensin II receptor blockers, aliskiren (a direct renin

inhibitor), and clonidine (a centrally acting drug). Only three studies reported data for total serious adverse events: two studies compared diuretics with calcium channel blockers and one with a direct renin inhibitor.

Compared to first-line beta-blockers, first-line thiazides probably result in little to no difference in *total mortality* (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.84 to 1.10; 5 trials, 18,241 participants; moderate-certainty), probably reduce *total cardiovascular events* (5.4% versus 4.8%; RR 0.88, 95% CI 0.78 to 1.00; 4 trials, 18,135 participants; absolute risk reduction (ARR) 0.6%, moderate-certainty), may result in little to no difference in *stroke* (RR 0.85, 95% CI 0.66 to 1.09; 4 trials, 18,135 participants; low-certainty), *CHD* (RR 0.91, 95% CI 0.78 to 1.07; 4 trials, 18,135 participants; low-certainty), or *heart failure* (RR 0.69, 95% CI 0.40 to 1.19; 1 trial, 6569 participants; low-certainty), and probably reduce *withdrawals due to adverse effects* (10.1% versus 7.9%; RR 0.78, 95% CI 0.71 to 0.85; 5 trials, 18,501 participants; ARR 2.2%; moderate-certainty).

Compared to first-line calcium channel blockers, first-line thiazides probably result in little to no difference in *total mortality* (RR 1.02, 95% CI 0.96 to 1.08; 7 trials, 35,417 participants; moderate-certainty), may result in little to no difference in *serious adverse events* (RR 1.09, 95% CI 0.97 to 1.24; 2 trials, 7204 participants; low-certainty), probably reduce *total cardiovascular events* (14.3% versus 13.3%; RR 0.93, 95% CI 0.89 to 0.98; 6 trials, 35,217 participants; ARR 1.0%; moderate-certainty), probably result in little to no difference in *stroke* (RR 1.06, 95% CI 0.95 to 1.18; 6 trials, 35,217 participants; moderate-certainty) or *CHD* (RR 1.00, 95% CI 0.93 to 1.08; 6 trials, 35,217 participants; moderate-certainty), probably reduce *heart failure* (4.4% versus 3.2%; RR 0.74, 95% CI 0.66 to 0.82; 6 trials, 35,217 participants; ARR 1.2%; moderate-certainty), and may reduce *withdrawals due to adverse effects* (7.6% versus 6.2%; RR 0.81, 95% CI 0.75 to 0.88; 7 trials, 33,908 participants; ARR 1.4%; low-certainty).

Compared to first-line ACE inhibitors, first-line thiazides probably result in little to no difference in *total mortality* (RR 1.00, 95% CI 0.95 to 1.07; 3 trials, 30,961 participants; moderate-certainty), may result in little to no difference in *total cardiovascular events* (RR 0.97, 95% CI 0.92 to 1.02; 3 trials, 30,900 participants; low-certainty), probably reduce *stroke* slightly (4.7% versus 4.1%; RR 0.89, 95% CI 0.80 to 0.99; 3 trials, 30,900 participants; ARR 0.6%; moderate-certainty), probably result in little to no difference in *CHD* (RR 1.03, 95% CI 0.96 to 1.12; 3 trials, 30,900 participants; moderate-certainty) or *heart failure* (RR 0.94, 95% CI 0.84 to 1.04; 2 trials, 30,392 participants; moderate-certainty), and probably reduce *withdrawals due to adverse effects* (3.9% versus 2.9%; RR 0.73, 95% CI 0.64 to 0.84; 3 trials, 25,254 participants; ARR 1.0%; moderate-certainty).

Compared to first-line alpha-blockers, first-line thiazides probably result in little to no difference in *total mortality* (RR 0.98, 95% CI 0.88 to 1.09; 1 trial, 24,316 participants; moderate-certainty), probably reduce *total cardiovascular events* (12.1% versus 9.0%; RR 0.74, 95% CI 0.69 to 0.80; 2 trials, 24,396 participants; ARR 3.1%; moderate-certainty) and *stroke* (2.7% versus 2.3%; RR 0.86, 95% CI 0.73 to 1.01; 2 trials, 24,396 participants; ARR 0.4%; moderate-certainty), may result in little to no difference in *CHD* (RR 0.98, 95% CI 0.86 to 1.11; 2 trials, 24,396 participants; low-certainty), probably reduce *heart failure* (5.4% versus 2.8%; RR 0.51, 95% CI 0.45 to 0.58; 1 trial, 24,316 participants; ARR 2.6%; moderate-certainty), and may reduce *withdrawals due to adverse effects* (1.3% versus 0.9%; RR 0.70, 95% CI 0.54 to 0.89; 3 trials, 24,772 participants; ARR 0.4%; low-certainty).

For the other drug classes, data were insufficient. No antihypertensive drug class demonstrated any clinically important advantages over first-line thiazides.

Authors' conclusions

When used as first-line agents for the treatment of hypertension, thiazides and thiazide-like drugs likely do not change total mortality and likely decrease some morbidity outcomes such as cardiovascular events and withdrawals due to adverse effects, when compared to beta-blockers, calcium channel blockers, ACE inhibitors, and alpha-blockers.

PLAIN LANGUAGE SUMMARY

What are the benefits and harms of diuretics given as a first treatment compared to other drug classes for hypertension (high blood pressure)?

Key messages:

- Thiazides and thiazide-like drugs (diuretics) probably decrease some adverse cardiovascular events compared to beta-blockers, calcium channel blockers, ACE inhibitors, and alpha-blockers when used as the first-line drug for the treatment of hypertension.

- Total mortality is probably not different between diuretics and the other drug classes.

- First-line diuretics likely reduce total cardiovascular events and heart failure compared to calcium channel blockers and alpha-blockers.

- First-line diuretics likely reduce withdrawals from the studies due to unwanted or harmful (adverse) effects compared to beta-blockers, calcium channel blockers, ACE inhibitors, and alpha-blockers.

What is hypertension (high blood pressure)?

Hypertension is defined using resting blood pressures: mild (140 to 159/90 to 99 mmHg), moderate (160 to 179/100 to 109 mmHg), and severe (180/110 mmHg or higher). Uncontrolled high blood pressure can lead to stroke, heart attack, heart failure, and kidney damage. Blood pressure-lowering drugs have been proven to reduce these adverse events in people aged 60 years and older with moderate to severe elevations of blood pressure; they also reduce stroke in adults under 60 years old with hypertension.

How is hypertension treated?

This review focused on blood pressure-lowering classes of drugs given as the initial drug treatment when lifestyle interventions are insufficient. The drug classes of interest include diuretics (e.g. hydrochlorothiazide, chlorthalidone); beta-blockers (e.g. propranolol, atenolol); calcium channel blockers (e.g. amlodipine, nifedipine); angiotensin-converting enzyme (ACE) inhibitors (e.g. lisinopril, enalapril); angiotensin receptor blockers (e.g. candesartan, losartan); renin inhibitors (e.g. aliskiren); alpha-blockers (e.g. doxazosin); and centrally acting drugs (e.g. clonidine).

What did we want to find out?

We wanted to find out whether the benefits and harms of diuretics given first for hypertension differed from other drug classes.

What did we do?

We searched for studies that compared first-line diuretics with other blood pressure-lowering drug classes in people with hypertension. We compared and summarized the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 20 studies that involved over 90,000 people with hypertension and lasted five years on average.

Main results

Mortality is probably not different between diuretics and the other drug classes when used in the first-line setting. First-line diuretics probably reduce cardiovascular events when compared to beta-blockers. First-line diuretics probably reduce cardiovascular events and heart failure when compared to calcium channel blockers. First-line diuretics probably reduce stroke slightly when compared to ACE inhibitors. First-line diuretics probably reduce total cardiovascular events, stroke, and heart failure when compared with alpha-blockers. Diuretics likely reduce withdrawals due to adverse effects when compared to beta-blockers, calcium channel blockers, ACE inhibitors, and alpha-blockers. There were not enough data to compare against angiotensin receptor blockers and renin inhibitors.

What are the main limitations of the evidence?

More head-to-head trials are needed comparing low-dose thiazides with angiotensin receptor blockers and renin inhibitors.

How up-to-date is the evidence?

The evidence is up-to-date to March 2021.

Summary of findings 1. First-line thiazides compared with first-line beta-blockers for hypertension in adults

First-line thiazides versus first-line beta-blockers for hypertension in adults

Patient or population: adults with hypertension
Setting: outpatients
Intervention: first-line thiazides
Comparison: first-line beta-blockers

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with beta-blockers	Risk with thiazides				
Total mortality Duration: 1 to 5.8 years	44 per 1000	42 per 1000 (37 to 48)	RR 0.96 (0.84 to 1.10)	18,241 (5 studies)	⊕⊕⊕◯ MODERATE[1]	Probably little to no difference (I^2 = 22%)
Total serious adverse events	—	—	—	—	—	None of the studies reported this outcome
Total cardiovascular events Duration: 1 to 5.8 years	54 per 1000	48 per 1000	RR 0.88 (0.78 to 1.00)	18,135 (4 studies)	⊕⊕⊕◯ MODERATE[1]	First-line diuretics probably lower cardiovascular events (I^2 = 44%) (ARR = 0.6%)
Total stroke Duration: 1 to 5.8 years	14 per 1000	12 per 1000 (9 to 15)	RR 0.85 (0.66 to 1.09)	18,135 (4 studies)	⊕⊕◯◯ LOW[1,2]	May be little to no difference (I^2 = 73%)
Total CHD Duration: 1 to 5.8 years	35 per 1000	32 per 1000	RR 0.91 (0.78 to 1.07)	18,135 (4 studies)	⊕⊕◯◯ LOW[1,2]	May be little to no difference (I^2 = 67%)
Total congestive heart failure Duration: 3.8 years	10 per 1000	7 per 1000 (4 to 12)	RR 0.69 (0.40 to 1.19)	6569 (1 study)	⊕⊕◯◯ LOW[1,3]	May be little to no difference
Withdrawals due to adverse effects	101 per 1000	79 per 1000	RR 0.78	18,501	⊕⊕⊕◯	First-line diuretics probably lower withdrawals due to adverse effects

Duration: 1 to 5.8 years		(0.72 to 0.86)	(0.71 to 0.85)	(5 studies)	MODERATE[2]	(I^2 = 91%) (ARR = 2.2%)

*__The risk in the thiazide group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CHD: coronary heart disease; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level because studies had notable levels of unclear or high risk of bias.
[2]Downgraded one level because of notable inconsistency between the outcomes of studies.
[3]Downgraded one level due to imprecision.

Summary of findings 2. First-line thiazides compared with first-line calcium channel blockers for hypertension in adults

First-line thiazides versus first-line calcium channel blockers for hypertension in adults

Patient or population: adults with hypertension
Setting: outpatients
Intervention: first-line thiazides
Comparison: first-line calcium channel blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with calcium channel blockers	Risk with thiazides				
Total mortality Duration: 1 to 5 years	109 per 1000	111 per 1000 (105 to 118)	RR 1.02 (0.96 to 1.08)	35,417 (7 studies)	⊕⊕⊕◯ MODERATE[1]	Probably little to no difference (I^2 = 0%)
Total serious adverse events Duration: 1.75 to 3 years	106 per 1000	116 per 1000 (103 to 131)	RR 1.09 (0.97 to 1.24)	7204 (2 studies)	⊕⊕◯◯ LOW[1,2]	May be little to no difference

						(I^2 = 80%)
Total cardiovascular events Duration: 1 to 5 years	143 per 1000	133 per 1000 (127 to 140)	RR 0.93 (0.89 to 0.98)	35,217 (6 studies)	⊕⊕⊕◯ MODERATE[1]	Probably lower (I^2 = 0%) (ARR=1.0%)
Total stroke Duration: 1 to 5 years	34 per 1000	36 per 1000 (32 to 40)	RR 1.06 (0.95 to 1.18)	35,217 (6 studies)	⊕⊕⊕◯ MODERATE[1]	Probably little to no difference (I^2 = 0%)
Total CHD Duration: 1 to 5 years	66 per 1000	66 per 1000 (61 to 71)	RR 1.00 (0.93 to 1.08)	35,217 (6 studies)	⊕⊕⊕◯ MODERATE[1]	Probably little to no difference (I^2 = 0%)
Total congestive heart failure Duration: 1 to 5 years	44 per 1000	32 per 1000 (29 to 36)	RR 0.74 (0.66 to 0.82)	35,217 (6 studies)	⊕⊕⊕◯ MODERATE[1]	Probably lower (I^2 = 10%) (ARR = 1.2%)
Withdrawals due to adverse effects Duration: 1 to 5 years	76 per 1000	62 per 1000 (57 to 68)	RR 0.81 (0.75 to 0.88)	33,908 (7 studies)	⊕⊕◯◯ LOW[1,2]	May be lower (I^2 = 74%) (ARR = 1.4%)

*__The risk in the thiazide group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ARR: absolute risk reduction; **CHD:** coronary heart disease; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

[1]Downgraded one level because studies had notable levels of unclear or high risk of bias.
[2]Downgraded one level because of notable inconsistency between the outcomes of studies.

Summary of findings 3. First-line thiazides compared with first-line ACE inhibitors for hypertension in adults

First-line thiazides versus first-line ACE inhibitors for hypertension in adults

Patient or population: adults with hypertension
Setting: outpatients
Intervention: first-line thiazides
Comparison: first-line ACE inhibitors

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ACE inhibitors	Risk with thiazides				
Total mortality Duration: 1 to 5 years	122 per 1000	122 per 1000 (116 to 130)	RR 1.00 (0.95 to 1.07)	30,961 (3 studies)	⊕⊕⊕○ MODERATE[1]	Probably little to no difference (I^2 = 0%)
Total serious adverse events	—	—	—	—	—	None of the studies reported this outcome
Total cardiovascular events Duration: 2.6 to 5 years	170 per 1000	165 per 1000	RR 0.97 (0.92 to 1.02)	30,900 (3 studies)	⊕⊕○○ LOW[1,2]	May be little to no difference (I^2 = 55%)
Total stroke Duration: 2.6 to 5 years	47 per 1000	41 per 1000 (37 to 46)	RR 0.89 (0.80 to 0.99)	30,900 (3 studies)	⊕⊕⊕○ MODERATE[1]	First-line thiazides probably lower total stroke slightly (I^2 = 0%) (ARR = 0.6%)
Total CHD Duration: 2.6 to 5 years	79 per 1000	82 per 1000	RR 1.03 (0.96 to 1.12)	30,900 (3 studies)	⊕⊕⊕○ MODERATE[1]	Probably little to no difference (I^2 = 21%)
Total congestive heart failure Duration: 4 to 5 years	45 per 1000	42 per 1000 (37 to 46)	RR 0.94 (0.84 to 1.04)	30,392 (2 studies)	⊕⊕⊕○ MODERATE[1]	Probably little to no difference (I^2 = 36%)
Withdrawals due to adverse effects Duration: 1 to 5 years	39 per 1000	29 per 1000 (25 to 33)	RR 0.73 (0.64 to 0.84)	25,254 (3 studies)	⊕⊕⊕○ MODERATE[1]	First-line thiazides probably lower withdrawals due to adverse effects (I^2 = 14%) (ARR = 1.0%)

*__The risk in the thiazide group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACE: angiotensin converting enzyme; **ARR:** absolute risk reduction; **CHD:** coronary heart disease; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

[1]Downgraded one level because studies had notable levels of unclear or high risk of bias.
[2]Downgraded one level because of notable inconsistency between the outcomes of studies.

Summary of findings 4. First-line thiazides compared with first-line alpha-blockers for hypertension in adults

First-line thiazides versus first-line alpha-blockers for hypertension in adults

Patient or population: adults with hypertension
Setting: outpatients
Intervention: first-line thiazides
Comparison: first-line alpha-blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with alpha-blockers	Risk with thiazides				
Total mortality Duration: 3.2 years	57 per 1000	56 per 1000 (50 to 62)	RR 0.98 (0.88 to 1.09)	24,316 (1 study)	⊕⊕⊕◯ MODERATE[1]	Probably little to no difference
Total serious adverse events	—	—	—	—	—	None of the studies reported this outcome
Total cardiovascular events Duration: 3 to 3.2 years	121 per 1000	90 per 1000	RR 0.74 (0.69 to 0.80)	24,396 (2 studies)	⊕⊕⊕◯ MODERATE[1]	First-line thiazides probably lower cardiovascular events (I^2 = 0%) (ARR = 3.1%)
Total stroke	27 per 1000	23 per 1000	RR 0.86	24,396	⊕⊕⊕◯	First-line thiazides probably lower stroke

Duration: 3 to 3.2 years		(20 to 27)	(0.73 to 1.01)	(2 studies)	MODERATE[1]	(I^2 = 29%) (ARR = 0.4%)
Total CHD Duration: 3 to 3.2 years	41 per 1000	40 per 1000	RR 0.98 (0.86 to 1.11)	24,396 (2 studies)	⊕⊕◯◯ LOW[1,2]	May be little to no difference (I^2 = 52%)
Total congestive heart failure Duration: 3.2 years	54 per 1000	28 per 1000 (24 to 31)	RR 0.51 (0.45 to 0.58)	24,316 (1 study)	⊕⊕⊕◯ MODERATE[1]	First-line thiazides probably lower heart failure (ARR = 2.6%)
Withdrawals due to adverse effects Duration: 1 to 3.2 years	13 per 1000	9 per 1000 (7 to 12)	RR 0.70 (0.54 to 0.89)	24,772 (3 studies)	⊕⊕◯◯ LOW[1,2]	First-line thiazides may reduce withdrawals due to adverse effects (I^2 = 82%) (ARR = 0.4%)

*__The risk in the thiazide group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ARR: absolute risk reduction; **CHD:** coronary heart disease; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level because studies had notable levels of unclear or high risk of bias.
[2]Downgraded one level because of notable inconsistency between the outcomes of studies.

BACKGROUND

Description of the condition

Elevated blood pressure (hypertension) is a chronic condition in which the blood pressure in the arteries is persistently elevated. It has been divided into three categories, based on resting blood pressures, measured in a standard way: mild hypertension (140 to 159/90 to 99 mmHg), moderate hypertension (160 to 179/100 to 109 mmHg), and severe hypertension (180/110 mmHg or higher) (James 2014). Most people with high blood pressure have no signs or symptoms and most have primary or essential hypertension, where there is no identifiable cause for the high blood pressure. Uncontrolled persistent resting high blood pressure increases the risk of stroke, heart attack, heart failure, and kidney damage (James 2014).

High blood pressure should initially be controlled by lifestyle changes, including eating a healthy diet with less salt, exercising regularly, quitting smoking, and maintaining a healthy weight. When these lifestyle changes are insufficient, treatment with antihypertensive drugs is recommended. Antihypertensive drugs have been proven to reduce mortality, stroke, myocardial infarction, and heart failure in adults 60 years of age and older with moderate to severe hypertension (Musini 2019), and to reduce stroke in adults under 60 (Musini 2017). Key guidelines do have an impact on how hypertension is managed globally (Whelton 2018; Williams 2018). However, they can be confusing for clinicians as they can be contradictory in their recommendations (Bakris 2019). We deliberately do not recommend any particular hypertension guideline, as all of the many available guidelines are conflicted to some degree due to funding and/or influence by the manufacturers of antihypertensive drugs (Ben-Eltriki 2021). These conflicts tend to lead to non-evidence-based overdiagnosis and overtreatment.

Description of the intervention

One of the major decisions involved in the management of patients with elevated blood pressure is which class of drug to choose to start with (first-line therapy). Presently, the available evidence is limited and lacks head-to-head comparisons of individual drug classes, which examine outcomes that are most important to patients with hypertension. There have been a number of systematic reviews assessing the effectiveness of antihypertensive therapy. However, most have used step care therapy and allowed the combination of different drug classes. Furthermore, they concentrated on overall effectiveness versus untreated controls (Collins 1990; Gueyffier 1996), or effectiveness in specific age groups (Insua 1994; MacMahon 1993; Musini 2017; Musini 2019; Thijs 1992). When different drug classes are combined in a systematic review, there is an underlying assumption that the lowering of blood pressure is independent of the drugs that are used and the mechanism by which decreased blood pressure is achieved. It is also possible that the pharmacological action by which a drug class lowers blood pressure will have additional effects in the body, which are independent of changes in blood pressure. These other actions, both known and unknown, could enhance or negate the benefits and harms of a drug and must be considered in the effect on different outcomes.

Thiazide diuretics are the most studied first-line drug class and appear to have some advantages over the other drug classes (Wright 1999; Wright 2018). Thiazide and thiazide-like diuretics are thus the most appropriate drug class to compare to other classes in head-to-head randomized controlled trials. The other classes include beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, alpha-adrenergic blockers, direct renin inhibitors, and centrally acting drugs.

How the intervention might work

Thiazide and thiazide-like diuretics: the blood pressure-lowering mechanism of action of thiazides is not fully understood. When administered acutely, thiazides lower blood pressure by causing diuresis, which reduces plasma volume and leads to a reduction in cardiac output. Chronic use of thiazides causes a reduction in blood pressure by lowering peripheral vascular resistance (vasodilation). Thiazides also may reduce blood pressure by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter (Duarte 2010). They also increase calcium reabsorption at the distal tubule. By lowering the sodium concentration in the tubule epithelial cells, thiazides indirectly increase the activity of the basolateral Na^+/Ca^{2+} antiporter, which facilitates the transport of Ca^{2+} from the epithelial cells into the renal interstitium. This movement of Ca^{2+} in turn decreases the intracellular Ca^{2+} concentration, which allows more Ca^{2+} to diffuse from the lumen of the tubules into epithelial cells via apical Ca^{2+}-selective channels (TRPV5). Thiazides are also thought to increase the reabsorption of Ca^{2+} by a mechanism involving the reabsorption of Na^+ and Ca^{2+} in the proximal tubule in response to Na^+ depletion. Some of this response may be due to augmentation of the action of parathyroid hormone (Longo 2010).

Beta-blockers: beta-blockers are competitive antagonists that block the receptor sites for the endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) on adrenergic beta receptors of the sympathetic nervous system. Some block activation of all types of β-adrenergic receptors and others are selective for one of the three known types of beta receptors, designated β_1, β_2 and β_3 receptors. β_1-adrenergic receptors are located mainly in the heart and in the kidneys; β_2-adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle; and β_3-adrenergic receptors are located in fat cells (Frishman 2005).

Angiotensin converting enzyme (ACE) inhibitors: ACE inhibitors block the conversion of angiotensin I (AI) to angiotensin II (AII). They thereby lower arteriolar resistance and increase venous capacity and lower resistance in blood vessels in the kidneys, and lead to increased excretion of sodium in the urine. Renin increases in concentration in the blood as a result of negative feedback of conversion of AI to AII. AI increases for the same reason; AII and aldosterone decrease. Bradykinin increases because of less inactivation by ACE (Dzau 1990).

Angiotensin II receptor blockers (ARBs): ARBs block the activation of AII AT_1 receptors. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces the production and secretion of aldosterone, among other actions. The combined effect reduces blood pressure (Rodgers 2001).

Calcium channel blockers: this class of antihypertensive drugs includes dihydropyridines and non-dihydropyridines. They reduce blood pressure through various mechanisms, including: acting on vascular smooth muscle and causing an increase in arterial diameter (vasodilation); acting on cardiac muscles, where they reduce the force of contraction of the heart; slowing down the conduction of electrical activity within the heart and thus reducing the heart rate; and blocking the calcium signal on adrenal cortex cells thus directly reducing aldosterone production (Katz 1986).

Alpha-adrenergic blockers: α_1 adrenergic receptor blockers inhibit the binding of norepinephrine to the α_1 receptors on the membrane of vascular smooth muscle cells. The primary effect of this inhibition is vasodilation, which decreases peripheral vascular resistance, leading to decreased blood pressure (Nash 1990).

Renin inhibitors: renin inhibitors bind the active site of the renin enzyme, thereby inhibiting its ability to cleave circulating angiotensinogen to AI and subsequently lowering circulating AI and AII concentrations (Shafiq 2008), leading to similar effects to the ACE inhibitors and ARBs.

Centrally acting drugs: these drugs act on the central nervous system to decrease sympathetic activity and reduce blood pressure. Examples include clonidine and alpha methyldopa.

Why it is important to do this review

A number of existing systematic reviews have compared first-line drugs versus placebo or no treatment; these reviews concluded that thiazide diuretics are the first-line therapy class associated with the best mortality and morbidity evidence (Psaty 1997; Wright 1999; Wright 2018). These findings would best be supported with a review of head-to-head randomized trials, where first-line thiazide diuretics are compared with other drug classes. Previous attempts to do this include a review, which pooled data from first-line drug treatment in antihypertensive trials (Collins 1990). These comparisons only included three trials that compared thiazides with beta-blockers; one of these trials was not appropriate for this comparison as both treatment arms received thiazides (IPPSH 1985). Psaty 2003 performed a network meta-analysis that combined direct and indirect comparisons of different first-line drug classes and concluded that thiazide diuretics were as good as or better than other antihypertensive classes. Other Cochrane Reviews have compared first-line beta-blockers (Wiysonge 2017), calcium channel blockers (Zhu 2021), or inhibitors of the renin angiotensin system (Chen 2018), with other first-line drug classes. Although some overlap exists between the comparisons in this Cochrane Review and other reviews (Chen 2018; Wiysonge 2017; Zhu 2021), this review is additive because it includes comparisons between diuretics and additional drug classes. Most importantly these reviews suggest that adverse cardiovascular outcomes are reduced more with first-line diuretics as compared to the other classes of drugs. Therefore, using first-line diuretics as the intervention is the most appropriate approach to this question.

This review builds on the previously published reviews Psaty 2003 and Wright 1999, with the objective of providing updated evidence about first-line diuretics versus other classes of antihypertensive drugs to assist guideline developers and clinicians in choosing the most appropriate first-line antihypertensive drug therapy based on the best available evidence of key effectiveness outcomes.

OBJECTIVES

Primary objective

To compare in head-to-head trials the effects of first-line diuretic drugs versus other classes of antihypertensive drugs on morbidity, mortality, and withdrawals due to adverse drug effects in patients with hypertension.

Secondary objectives

To compare the percentage of patients requiring dose titration, addition of a second or third drug, and switching to other therapy.

To compare the blood pressure-lowering efficacy at one year in the two groups.

METHODS

Criteria for considering studies for this review

Types of studies

Trials were eligible if they:

1. were randomized controlled trials (RCTs); quasi-randomized trials were not eligible for inclusion;
2. were of at least one year duration;
3. had study data that could be analyzed based on the intention-to-treat principle;
4. presented morbidity and mortality data that compared first-line diuretics head-to-head with one or more other first-line antihypertensive therapies.

Types of participants

Participants had to have a baseline resting blood pressure of at least 140 mmHg systolic or a diastolic blood pressure of at least 90 mmHg measured in a standard way on at least two occasions. Trials had to be limited to patients with elevated blood pressure or separately report outcome data on patients with elevated blood pressure as defined above.

Trials were not limited by any other factor or baseline risk. We assumed that age and co-morbidities do not affect the relative risk reduction associated with drug treatment.

Types of interventions

Randomized controlled trials had to include treatment that was clearly defined as specific first-line antihypertensive therapy: thiazide, thiazide-like, or loop diuretics versus beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, alpha-adrenergic blockers, direct renin inhibitors, or centrally acting antihypertensive drugs. The majority (> 70%) of the patients in the treatment and control group should have been taking the first-line drug class of interest after one year. Only initial combined therapy with potassium-sparing diuretics (triamterene or amiloride) was allowed. These were included as there is evidence that they do not affect blood pressure (Heran 2012b). Supplemental drugs from other drug classes of interest were only allowed as stepped therapy in both groups, and only as long as they were not taken by over 50% of the patients. We assumed that these supplemental drugs may not systematically interact to affect the occurrence of the endpoints

studied. We also assumed that there are no major differences in the effects of different drugs in the defined classes. All trials comparing a first-line diuretic with one or more other first-line antihypertensive drug classes were included irrespective of the dose used.

Types of outcome measures

Primary outcomes

1. Total mortality (death from all causes)
2. Total serious adverse events (patients with at least one serious adverse event)
3. Total number of people with at least one cardiovascular event including total stroke and total coronary heart disease (CHD) plus hospitalization or death from congestive heart failure and other significant vascular events such as ruptured aneurysms (does not include angina, transient ischemic attacks (TIAs), revascularization procedures or accelerated hypertension)
4. Total stroke including fatal and non-fatal strokes
5. Total CHD including fatal and non-fatal myocardial infarction and sudden or rapid cardiac death
6. Total congestive heart failure (death or hospitalization for heart failure)
7. Total withdrawals due to adverse effects

We analyzed all the primary outcomes as dichotomous outcomes, i.e. the number of people with at least one event. We excluded trials if they did not report any of the primary outcomes. When the trials did not report primary outcomes that exactly matched the above definitions, decisions by consensus among review authors were made based on maximizing the inclusion of the data and maintaining concordance with how the data were handled in previous systematic reviews (Chen 2018; Psaty 2003; Wiysonge 2017; Wright 1999). We assumed that the effects of antihypertensive treatment on outcomes would be independent of whether elevated blood pressure was defined in terms of systolic or diastolic pressure.

Secondary outcomes

1. Percentage of patients requiring dose titration and addition of a second or third drug
2. Percentage of patients switching to other antihypertensive therapies
3. Systolic and diastolic blood pressure at one year

Search methods for identification of studies

Electronic searches

We searched the following databases for randomized controlled trials (RCTs) without language or publication status restrictions:

- the Cochrane Hypertension Specialized Register via the Cochrane Register of Studies (top-up search 27 June 2022);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 2) via the Cochrane Register of Studies (searched 25 March 2021);
- MEDLINE Ovid (from 1998; searched 25 March 2021);
- Embase Ovid (from 1998; searched 25 March 2021);
- US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov) (searched 26 March 2021);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 26 March 2021).

Searches of MEDLINE and Embase were limited to 1998 onward (using the .dt. and.dc. commands, respectively) as it was assumed that pre-1998 studies would have been identified by previous related systematic reviews (Psaty 2003; Wright 1999), and by searches of CENTRAL and the Cochrane Hypertension Specialized Register. In addition, we assessed the lists of references identified by the three Cochrane systematic reviews comparing first-line therapy with beta-blockers (Wiysonge 2017), calcium channel blockers (Zhu 2021), and drugs inhibiting the renin-angiotension system (Chen 2018) with other classes of antihypertensive therapy to confirm that no trials comparing either of these classes with diuretics were missed. The Hypertension Specialized Register is updated weekly with new results from Ovid MEDLINE and Ovid Embase and updated monthly with searches of CENTRAL. Register searches for this review did not contain any exclusion commands.

The Information Specialist modeled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021)). We present the search strategies in Appendix 1.

Searching other resources

The Cochrane Hypertension Information Specialist searched the Hypertension Specialized Register segment (which includes searches of MEDLINE and Epistemonikos for systematic reviews) to retrieve existing systematic reviews relevant to our topic, so that we could scan their reference lists for additional trials. The Specialized Register also includes searches of CAB Abstracts & Global Health, CINAHL, ProQuest Dissertations & Theses, and Web of Knowledge.

We checked the bibliographies of included studies and relevant systematic reviews, including recent reviews comparing thiazide or thiazide-like diuretics to other antihypertensive classes, to ensure identification of all relevant trials.

Where necessary, we contacted authors of key papers and abstracts to request additional information about their trials.

Data collection and analysis

Selection of studies

One review author (MR) screened the titles and abstracts resulting from the search strategies. We rejected articles on the initial screen only if it could be determined from the title or the abstract that the article was not a report of a randomized controlled trial (RCT) assessing diuretic monotherapy in a head-to-head comparison with another antihypertensive class in patients with hypertension. Two of three review authors (LP, MR, or JW) independently assessed the full-text articles of studies that passed the initial screen according to the inclusion criteria listed in Criteria for considering studies for this review, with disagreements resolved through discussion or the involvement of a third review author (JW). We excluded trials that met the minimum inclusion criteria but only reported systolic and diastolic blood pressure outcomes.

Data extraction and management

Data extraction was completed by two review authors independently (MR, LP, or JW), cross-checked and compared whenever possible to data from previously published meta-analyses (Chen 2018; Psaty 2003; Wiysonge 2017; Wright 1999; Zhu 2021). The data extraction form included details of the study design, duration of treatment, baseline characteristics, number of patients lost to follow-up, interventions, and outcomes.

Assessment of risk of bias in included studies

We assessed risk of bias in each trial using a modified version of Cochrane's tool for assessing risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Six of the domains assessed were sequence generation, allocation concealment, blinding, incomplete outcome data, and within-study selective outcome reporting. At least two of three review authors (LP, MR, or JW) independently assessed the risk of bias for each study based on these domains with ratings of 'low risk of bias', 'high risk of bias', and 'unclear risk'. We resolved discrepancies by discussion and consensus.

We also assessed trials for the use of supplemental drugs. We regarded high-quality trials (low risk of bias) to be those designed such that the supplemental drugs for blood pressure not controlled by the first-line drugs were the same for each arm of the trial. In this way, any difference in outcomes could be attributed to the first-line drug. We judged trials designed to allow different supplemental drugs or in which the algorithms for treatment or stepped care with supplemental drug classes differed between comparative groups to be at high risk of bias.

Furthermore, we assessed trials for the presence of industry sponsorship (Lundh 2017). We considered studies that were clearly funded by a pharmaceutical company to have a high risk of bias. We judged studies with no clear industry sponsorship, but with authors who disclosed associations with pharmaceutical companies, to have an unclear risk of bias. We judged studies with no evidence of funding by a pharmaceutical company or author ties to pharmaceutical companies to have a low risk of bias.

Measures of treatment effect

Dichotomous data

We assessed dichotomous outcomes (total mortality, total serious adverse events, total cardiovascular events, total fatal and non-fatal stroke, total coronary heart disease (CHD), total congestive heart failure, withdrawals due to adverse effects, dose titration and the addition of second or third drugs, and switching therapies) using the risk ratio (RR), along with the 95% confidence interval (CI).

Continuous data

We assessed continuous data (systolic and diastolic blood pressure) using the mean difference (MD) along with the 99% CI.

Unit of analysis issues

Studies with multiple treatment groups

We did not expect to find cluster-RCTs for this clinical question as it would be very difficult to cluster by physician. Cross-over RCTs are not possible because of the one-year duration requirement. We assessed studies with multiple treatment groups (ALLHAT 2000/2002; Materson 1993) using the strategy of including each pair-wise comparison separately according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not undertake a comparison of diuretics with all other antihypertensive drugs pooled to avoid double-counting the first-line diuretic group.

We attempted to include people with at least one event for each of the outcomes. However, in studies such as ALLHAT 2000/2002, where it was not entirely clear, we assumed that the data reported were people with at least one event and not total events.

Dealing with missing data

When published articles did not provide data for specific outcomes or provide sufficient detail to permit full assessment, we contacted the authors. Specifically, we did this and received additional data for the PREVER-treatment 2016 trial.

When data were reported only as graph-based images and not numerically, we estimated values following analysis with an imaging software (Rohatgi 2021).

Several studies described using an intention-to-treat (ITT) analysis (ALLHAT 2000/2002; ALPINE 2003; ANBP2 2003; DAPHNE 2002; HAPPHY 1987; INSIGHT 2000; MIDAS 1996; MRC 1985; MRC 1992; NESTOR 2004; PHYLLIS 2004; PREVER-treatment 2016; SHELL 2003; VHAS 1997). In most cases, this was defined as the analysis of all randomized patients regardless of how long they remained in the trial (note that some studies further specified that one study visit or one treatment was required post-randomization), and used last observed data with no declared strategy for imputing missing data. The PREVER-treatment 2016 trial did state that it included imputed estimates from patients who were lost to follow-up or who had minor protocol deviations; no further information on how estimates were imputed was provided.

Assessment of heterogeneity

We assessed heterogeneity of treatment effect between the trials using a standard Chi^2 test for heterogeneity. We applied the fixed-effect model to obtain summary statistics of pooled trials. We used the I^2 statistic to estimate the percentage of variability due to heterogeneity rather than sampling error. If substantial heterogeneity was present (I^2 value greater than 50%), then we explored reasons for heterogeneity using sensitivity analyses (Sensitivity analysis). These included the effect of small trials, the effect of supplementary drugs, the effect of high doses of thiazides, and the effect of thiazide or thiazide-like drugs.

Assessment of reporting biases

We did not create funnel plots as there were fewer than 10 trials for each comparison. In future updates, if there are more than 10 trials in a comparison we will create funnel plots to identify evidence of small-study effects by visual inspection of asymmetry and by Egger's test (Higgins 2021).

Data synthesis

We conducted data synthesis and analyses using the Cochrane Review Manager software, RevMan 5.4 (RevMan 2020). Quantitative analyses of outcomes were based on ITT results, where possible. We used a Mantel Haenszel fixed-effect model for dichotomous outcomes, which we presented as a RR with 95% CI. We chose

this model a priori because we anticipated that we would have large and small trials and we wanted the most weight to go to the larger trials. When substantial heterogeneity was present (I^2 > 50%) we explored this using sensitivity analysis. We calculated absolute risk reduction (ARR) = risk difference x 100 and to number needed to treat for an additional beneficial outcome (NNTB) = 1/risk difference for outcomes that had moderate or higher certainty between diuretics and comparators. Continuous outcomes such as systolic and diastolic blood pressure are presented as a MD with 99% CI using an inverse variance fixed-effect model. If the trial did not report the within-study variance for decrease in blood pressure (ANBP2 2003; INSIGHT 2000; PHYLLIS 2004; SHELL 2003; VA 1982), we imputed the standard deviation (SD) from the average SD from the other trials. This imputation is acknowledged as a limitation, thus we reported the 99% CI instead of the standard 95% CI.

The data synthesis methods listed here differ from the original protocol (Reinhart 2011). These changes were approved following a review of updated analytical standards for meta-analysis as well as discussion and consensus among the review authors.

Subgroup analysis and investigation of heterogeneity

The review protocol noted that results of trials restricted to patients with isolated systolic hypertension would be analyzed as a separate group; however, only one small study (Tresukosol 2005; N = 200) included only patients with isolated systolic hypertension and this subgroup analysis was therefore not possible.

Sensitivity analysis

To test the robustness of our results, we performed pre-defined sensitivity analyses. We evaluated the effect of removing the largest trial (ALLHAT 2000/2002). We also investigated the effects of removing small trials (N < 1000 in each comparison). We tested the effect of supplemental drugs by first removing trials without supplemental drugs. We then assessed the effect further by removing trials where different supplemental drug classes or doses were allowed in each arm.

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro GDT software to present the summary of findings tables (GRADEpro GDT). As planned, we included all seven primary outcomes: total mortality, total serious adverse events, total cardiovascular events, total stroke, total coronary heart disease, total congestive heart failure, and withdrawals due to adverse events for four clinically important comparisons: first-line thiazides versus first-line beta-blockers, first-line thiazides versus first-line calcium channel blockers, first-line thiazides versus first-line ACE inhibitors, and first-line thiazides versus first-line alpha-blockers.

We considered five factors in grading the overall certainty of evidence: limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results, and high probability of publication bias. This approach specifies four levels of certainty: high, moderate, low, and very low certainty. The highest certainty rating is initially assigned to randomized trial evidence and may be downgraded by one level for each factor, up to a maximum of three levels for all factors. If there are severe problems for any one factor (when assessing limitations in study design and implementation, in concealment of allocation, loss of blinding, or attrition over 50% of participants during follow-up), randomized trial evidence may fall by two levels due to that factor alone.

RESULTS

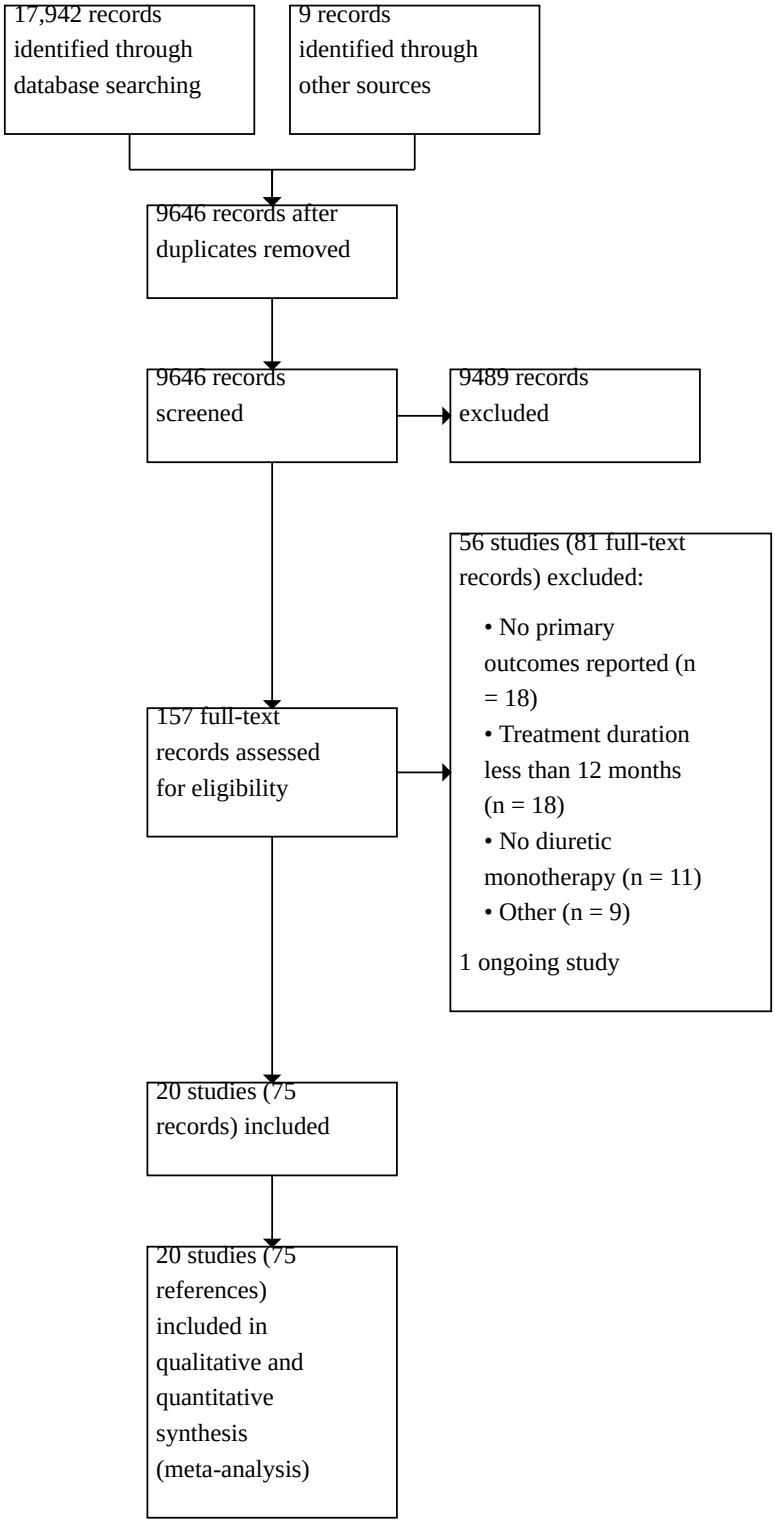
Description of studies

This review includes all randomized head-to-head trials of at least one year duration comparing first-line diuretics with other individual antihypertensive drug classes and reporting morbidity and mortality outcomes.

Results of the search

Electronic searches up to March 2021 retrieved 9646 unique, de-duplicated records. Of these 9646 records, we considered 157 full-text records potentially eligible after primary screening, and 20 studies (randomizing > 90,000 participants) met the inclusion criteria following the full-text screen (Figure 1). These studies include the nine trials that met the inclusion criteria and had been published prior to 1998 from an earlier systematic review (Wright 1999). We also identified one ongoing study (NCT02217852) (see Characteristics of ongoing studies). A top-up search of the Cochrane Hypertension Specialized Register to June 2022 retrieved 51 unique records, but did not yield additional included studies.

Figure 1.



Included studies

We included a total of 20 parallel-group randomized trials with 26 comparator arms in the review (see Characteristics of included studies). Study sample size ranged from fewer than 100 participants (DAPHNE 2002) to over 40,000 participants (ALLHAT 2000/2002); most studies had at least 500 participants and nine had over 1000 participants. Nearly all the studies took place in Western Europe and North America, except for three studies conducted in Japan (NICS-EH 1999), Australia (ANBP2 2003), and Brazil (PREVER-treatment 2016). All included studies enrolled participants with primary hypertension, and some assessed participants who had additional pre-specified comorbidities or cardiovascular risk factors such as diabetes (ALLHAT 2000/2002; DAPHNE 2002; NESTOR 2004; PHYLLIS 2004). The average participant's age in most included studies was 50 to 60 years, although some trials specifically assessed participants who were older (55 years and older: ALLHAT 2000/2002; ANBP2 2003; INSIGHT 2000; NICS-EH 1999; Tresukosol 2005; SHELL 2003). Five studies were restricted to males (Berglund 1981; DAPHNE 2002; HAPPHY 1987; Materson 1993; VA 1982); the remaining studies had both male and female participants.

Fifteen studies used first-line thiazide diuretics: in 11 studies the drug was hydrochlorothiazide (ALPINE 2003; ANBP2 2003; DAPHNE 2002; INSIGHT 2000; Materson 1993; MIDAS 1996; MRC 1992; PHYLLIS 2004; Schmieder 2009; Tresukosol 2005; VA 1982); in two it was bendrofluazide (Berglund 1981; MRC 1985); in one it was trichlormethiazide (NICS-EH 1999); and in one it was either hydrochlorothiazide or bendrofluazide (HAPPHY 1987). Five studies used first-line thiazide-like diuretics: chlorthalidone (ALLHAT 2000/2002; PREVER-treatment 2016; SHELL 2003; VHAS 1997) and indapamide (NESTOR 2004). The largest trial, ALLHAT 2000/2002, used chlorthalidone, therefore the total number of participants treated with a thiazide-like diuretic was similar to the number treated with a thiazide diuretic. First-line thiazide and thiazide-like diuretics were compared with the following first-line antihypertensive drugs: calcium channel blockers (eight studies: ALLHAT 2000/2002; INSIGHT 2000; Materson 1993; MIDAS 1996; NICS-EH 1999; SHELL 2003; Tresukosol 2005; VHAS 1997), beta-blockers (six studies: Berglund 1981; HAPPHY 1987; Materson 1993; MRC 1985; MRC 1992; VA 1982), ACE inhibitors (five studies: ALLHAT 2000/2002; ANBP2 2003; Materson 1993; NESTOR 2004; PHYLLIS 2004), alpha-adrenergic blockers (three studies: ALLHAT 2000/2002; DAPHNE 2002; Materson 1993), angiotensin II receptor blockers (two studies: ALPINE 2003; PREVER-treatment 2016), direct renin inhibitor (Schmieder 2009), and a centrally acting drug, clonidine (Materson 1993).

The duration of follow-up ranged from one year (six trials, ALPINE 2003; Berglund 1981; Materson 1993; NESTOR 2004; Schmieder 2009; VA 1982) to 5.8 years in the longest trial (MRC 1992). Five trials were five years or longer in duration (ALLHAT 2000/2002; MRC 1985; MRC 1992; NICS-EH 1999; SHELL 2003). In all trials except one, the drugs were administered in standard doses once daily in the morning. In the one exception, the drugs were administered twice daily (MIDAS 1996). The thiazide or thiazide-like doses were low-dose except for three older trials where they were high-dose (HAPPHY 1987; MRC 1985; VA 1982). High-dose thiazides were standard therapy at the time these trials were conducted. The details of the drug doses are provided in the Characteristics of included studies table.

All included studies reported at least one primary outcome of interest and the most frequently reported outcomes included total mortality (16 studies), withdrawals due to adverse effects (16 studies), total CHD events (15 studies), total fatal and non-fatal stroke events (14 studies), and total cardiovascular events (13 studies). Studies that reported changes in blood pressure but no other outcomes of interest were not included in this review.

Excluded studies

Fifty-six excluded studies and the reasons for exclusion are described in the Characteristics of excluded studies table. The trial being less than 12 months in duration was a common reason for exclusion, occurring in 18 studies (Cho 2008; Cooper-DeHoff 2010; Ebbs 2001; GENRES 2007; Iyalomhe 2014; Jordan 2012; Khan 2008; Klingbeil 2000; LIVE 1998; Mann 2002; Morgan 2004; Oshchepkova 2007; PEAR 2012; Pool 2009; Rasmussen 2006; SALT 2007; Schwartz 2013; Yasuda 2015). An equally common reason was that the study did not report any primary outcome. This was the reason in 18 studies (AVEC 2012; Caruso 2004; Galzerano 2004; Grassi 2006; Mahmud 2009; Posadzy-Malaczynska 2014; Schram 2005; Shionoiri 2000; Sierra 2004; SPREAD 2006; Stritzke 2010; Tedesco 1998; Tedesco 1999; Trimarco 2011; Trimarco 2015; Veronesi 2007; Wilson 1963; Yogiantoro 2000). The third most common reason was that the study did not have or report data for a diuretic monotherapy arm. This was the reason in 11 studies (Appel 2010; Bakris 2010; Bebb 2007; CONVINCE 2003; COSMO-CKD 2014; LIFE 2002; NORDIL 2000; PROGRESS 2001; STOP-Hypertension-2 1999; Syst-Eur 1997; VADT 2011).

Neaton 1993 was identified as a study that met the inclusion criteria for this review. This study compared treatments from five different antihypertensive drug classes, including the thiazide-like diuretic chlorthalidone, in male and female patients with hypertension for an average follow-up of 4.4 years. The clinical event data, however, were not reported separately for the intervention arms, and when contacted the authors refused to provide the data separately per intervention arm. Should these data be received in the future, this study will be included in an update of this review.

Risk of bias in included studies

A summary of the assessment of risk of bias of the included studies is shown in Figure 2 and Figure 3. We judged many of the studies to have an unclear risk of bias. Several of the included studies were published prior to the introduction of standardized reporting methods for clinical trials, and lacked sufficient detail for an adequate bias assessment.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

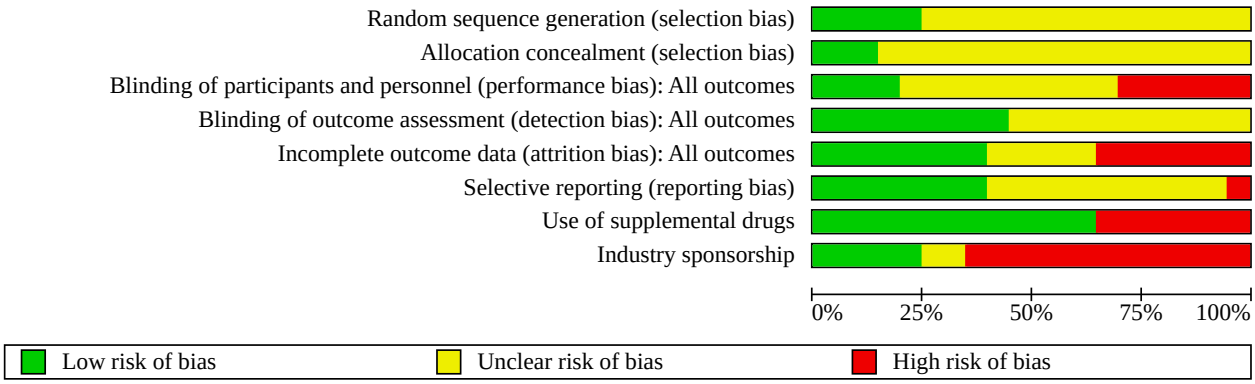


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

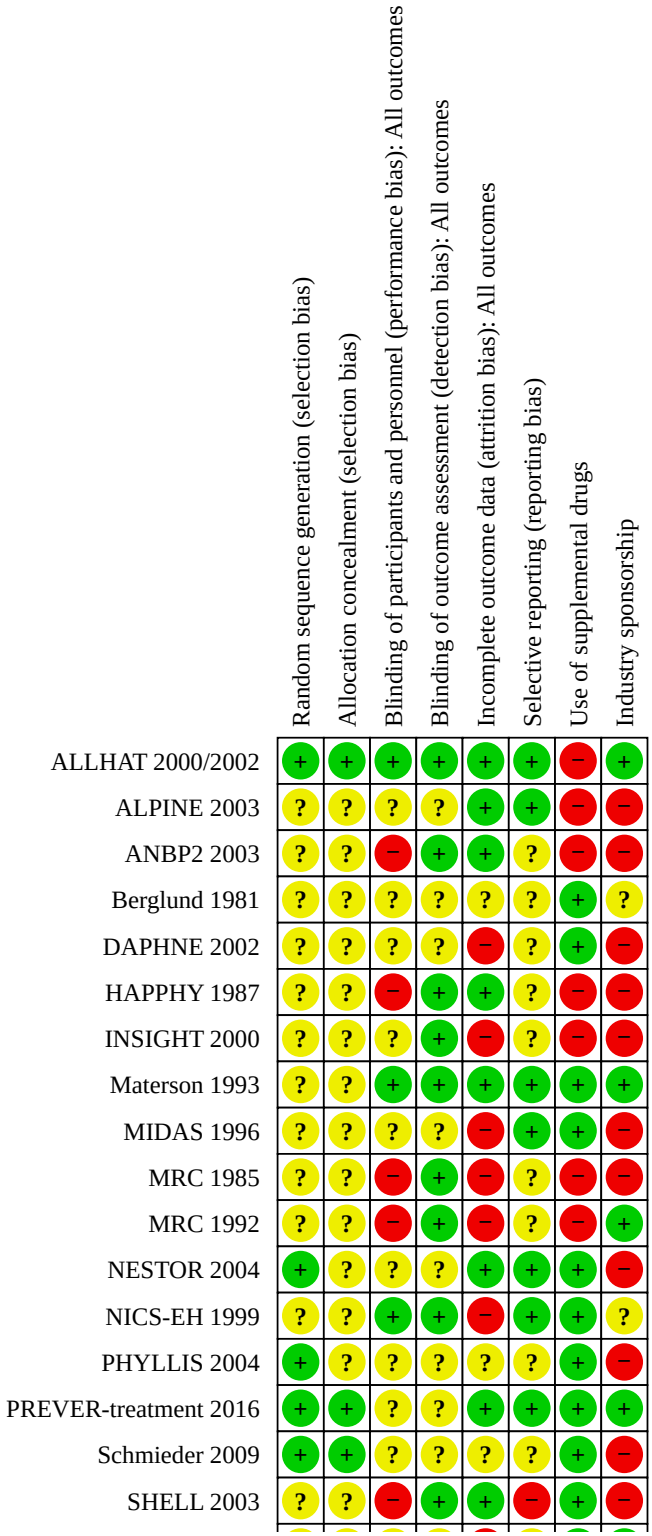
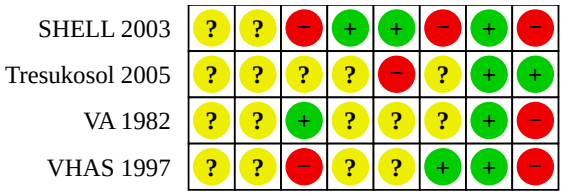


Figure 3. (Continued)



Allocation

Treatment allocation by random sequence generation was adequately described and had a low risk of bias in five of the included studies (ALLHAT 2000/2002; NESTOR 2004; PHYLLIS 2004; PREVER-treatment 2016; Schmieder 2009). Of these, only three studies had an adequate description of allocation concealment (ALLHAT 2000/2002; PREVER-treatment 2016; Schmieder 2009). The remaining studies had an unclear risk of allocation bias as they did not have a detailed description of the randomization procedure or method of allocation concealment.

Blinding

Either study personnel alone (MRC 1985; MRC 1992), or both patients and study personnel (ANBP2 2003; HAPPHY 1987; SHELL 2003; VHAS 1997), were unblinded to treatment allocation in six trials, leading to a high risk of bias assessment for blinding. We judged blinding to be adequate in four studies (ALLHAT 2000/2002; Materson 1993; NICS-EH 1999; VA 1982), with all other studies judged to have an unclear risk of bias, which in many cases was because of insufficient details describing the blinding protocol. Three studies used a double-blind design for the original treatment assignment but any add-on treatment was undertaken in an open-label fashion without clear rationale; we judged these studies to have an unclear risk of bias (NESTOR 2004; PHYLLIS 2004; PREVER-treatment 2016).

Outcome assessors were blind to treatment allocation in eight studies (ANBP2 2003; HAPPHY 1987; INSIGHT 2000; Materson 1993; MRC 1985; MRC 1992; NICS-EH 1999; SHELL 2003). The remaining studies had insufficient information for outcome assessment blinding and we this judged the risk of bias to be unclear.

Incomplete outcome data

We judged the majority of included studies to have a low risk of bias for incomplete outcome data; intention-to-treat analysis was used, and dropout numbers were small and generally balanced between the treatment groups. We assessed a high risk of bias for the NICS-EH 1999 and Tresukosol 2005 studies; the former had over 50% of patients discontinue and both used a per-protocol analysis rather than intention-to-treat. We graded some studies as having an unclear risk of bias, as it was unclear whether or not the intention-to-treat analysis was carried out properly. Some studies failed to report data on discontinuation.

Selective reporting

A protocol was not available for the majority of studies and the risk of bias therefore remained unclear. For all studies that did have an accessible protocol (ALLHAT 2000/2002; INSIGHT 2000; NESTOR 2004; NICS-EH 1999; VHAS 1997), we found no evidence of selective reporting. In the SHELL 2003 study, a protocol was not available but one of the secondary outcomes listed in the study methods was not reported in the results, thus we graded the study as having a high risk of bias for selective reporting.

Other potential sources of bias

We identified a high risk of bias resulting from inconsistent use of supplemental drugs in seven studies (ALPINE 2003; ANBP2 2003; HAPPHY 1987;INSIGHT 2000; MRC 1985; MRC 1992; SHELL 2003). We judged the remaining studies to have a low or unclear risk of bias because of either consistent add-on treatment across all groups or no add-on treatment permitted.

We also examined the role of industry sponsorship. Twelve studies were sponsored by a for-profit company of the comparator drug and we considered them to have a high risk of bias (ALPINE 2003; ANBP2 2003; DAPHNE 2002; HAPPHY 1987; INSIGHT 2000; MIDAS 1996; NESTOR 2004; PHYLLIS 2004; Schmieder 2009; SHELL 2003; VA 1982; VHAS 1997). We considered six studies to have a low risk of bias (ALLHAT 2000/2002; Materson 1993; MRC 1985; MRC 1992; PREVER-treatment 2016; Tresukosol 2005); two studies had insufficient information regarding sponsorship and we thus judged them to have an unclear risk of bias (Berglund 1981; NICS-EH 1999).

Effects of interventions

See: **Summary of findings 1** First-line thiazides compared with first-line beta-blockers for hypertension in adults; **Summary of findings 2** First-line thiazides compared with first-line calcium channel blockers for hypertension in adults; **Summary of findings 3** First-line thiazides compared with first-line ACE inhibitors for hypertension in adults; **Summary of findings 4** First-line thiazides compared with first-line alpha-blockers for hypertension in adults

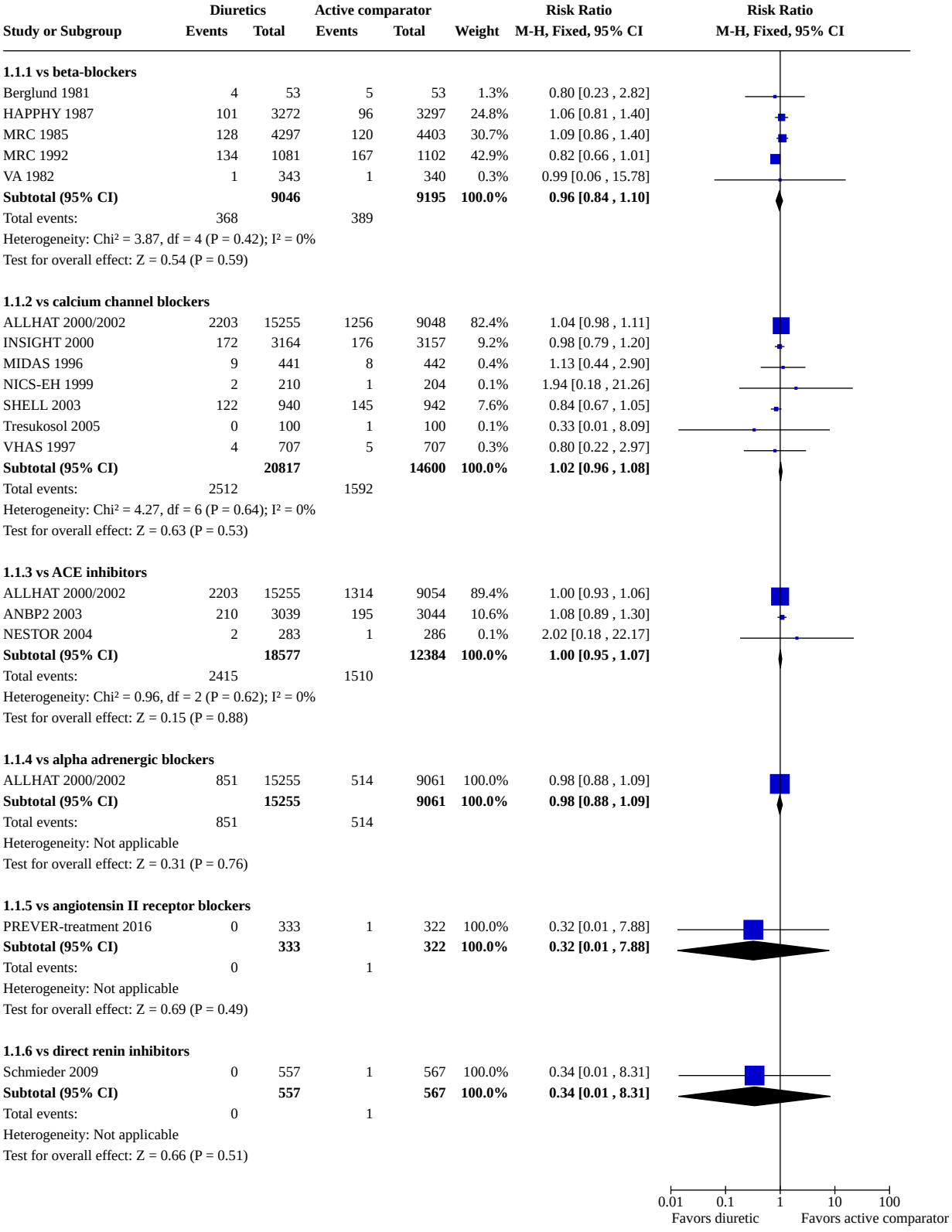
First-line diuretics versus other classes of antihypertensive drugs

Total mortality

Total mortality was reported in 16 out of 20 studies (Analysis 1.1; Figure 4). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. Mortality was similar when first-line diuretics were compared with beta-blockers (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.84 to 1.10; $Chi^2 = 3.87$ (P = 0.42); $I^2 = 0\%$; 5 studies, 18,241 participants; moderate-certainty evidence) (Berglund 1981; HAPPHY 1987; MRC 1985; MRC 1992; VA 1982), calcium channel blockers (RR 1.02, 95% CI 0.96 to 1.08; $Chi^2 = 4.27$ (P = 0.64); $I^2 = 0\%$; 7 studies, 35,417 participants; moderate-certainty evidence) (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; Tresukosol 2005; VHAS 1997), angiotensin converting enzyme (ACE) inhibitors (RR 1.00, 95% CI 0.95 to 1.07; $Chi^2 = 0.96$ (P = 0.62); $I^2 = 0\%$; 3 studies, 30,961 participants; moderate-certainty evidence) (ALLHAT 2000/2002; ANBP2 2003; NESTOR 2004), alpha-adrenergic blockers

(RR 0.98, 95% CI 0.88 to 1.09; 1 study, 24,316 participants; moderate-certainty evidence) (ALLHAT 2000/2002); angiotensin II receptor blockers (RR 0.32, 95% CI 0.01 to 7.88; 1 study, 655 participants) (PREVER-treatment 2016); and direct renin inhibitors (RR 0.34, 95% CI 0.01 to 8.31; 1 study, 1124 participants) (Schmieder 2009).

Figure 4. Forest plot of comparison: 1 First-line thiazides vs active comparators: primary outcomes, outcome: 1.1 Total mortality.



Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, total mortality remained similar between first-line diuretics and calcium channel blockers (RR 0.92, 95% CI 0.79 to 1.07; 6 studies, 11,114 participants), and between first-line diuretics and ACE inhibitors (RR 1.08, 95% CI 0.90 to 1.31; 2 studies, 6652 participants). This sensitivity analysis was not possible for comparisons with beta-blockers or alpha-blockers. When small trials (< 1000 participants in each comparison) were excluded, leaving ALLHAT 2000/2002, ANBP2 2003, HAPPHY 1987, INSIGHT 2000, MRC 1985, MRC 1992, Schmieder 2009, SHELL 2003, and VHAS 1997, total mortality remained similar between first-line diuretics and beta-blockers (RR 0.96, 95% CI 0.84 to 1.11; 3 studies, 17,452 participants), first-line diuretics and calcium channel blockers (RR 1.02, 95% CI 0.96 to 1.08; 4 studies, 33,920 participants), and between first-line diuretics and ACE inhibitors (RR 1.00, 95% CI 0.95 to 1.07; 2 studies, 30,392 participants). This analysis was not possible for alpha-blockers.

Supplemental drugs

In five trials, no supplemental drugs were allowed (Berglund 1981; DAPHNE 2002; Materson 1993; NICS-EH 1999; VA 1982). When they were deselected, mortality was unaffected between first-line diuretics and beta-blockers (RR 0.96, 95% CI 0.84 to 1.11; 4 studies, 18,135 participants) and between first-line diuretics and calcium channel blockers (RR 1.02, 95% CI 0.96 to 1.08; 6 studies, 35,003 participants). This analysis was not possible for ACE inhibitors and alpha-blockers. When trials where different supplemental drug classes were allowed in each arm were removed (ALLHAT 2000/2002; ALPINE 2003; ANBP2 2003; HAPPHY 1987; INSIGHT 2000; MRC 1985; MRC 1992), total mortality remained similar between first-line diuretics and beta-blockers (RR 0.83, 95% CI 0.26 to 2.61; 2 studies, 789 participants), first-line diuretics and calcium channel blockers (RR 0.86, 95% CI 0.69 to 1.06; 5 studies, 4795 participants), and between first-line diuretics and ACE inhibitors (RR 2.02, 95% CI 0.18 to 22.17; 1 study, 569 participants). This analysis was not possible for alpha-blockers.

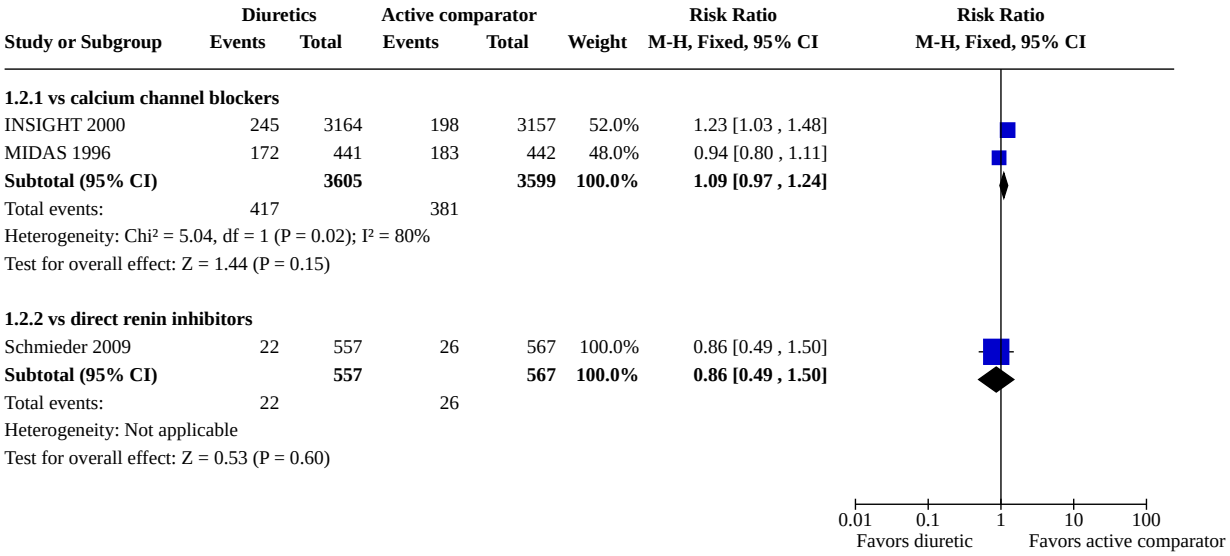
Dosage of thiazides

In a sensitivity analysis exploring the cause of heterogeneity, we deselected the three trials where the thiazide dose was high (HAPPHY 1987; MRC 1985; VA 1982). This only affected the beta-blocker comparison and total mortality became numerically reduced for the trials with low-dose thiazides (RR 0.82, 95% CI 0.66 to 1.01; 2 studies, 2289 participants).

Total serious adverse events

In total, only three studies reported data for total serious adverse events (INSIGHT 2000; MIDAS 1996; Schmieder 2009), which was defined as participants who experienced one or more serious adverse events. Two of these studies compared diuretics with calcium channel blockers (RR 1.09, 95% CI 0.97 to 1.24; Chi^2 = 5.04 (P = 0.02); I^2 = 80%; 2 studies, 7204 participants; low-certainty evidence) (INSIGHT 2000; MIDAS 1996), and one trial compared a diuretic to a direct renin inhibitor (RR 0.86, 95% CI 0.49 to 1.50; 1 study, 1124 participants) (Analysis 1.2; Figure 5) (Schmieder 2009).

Figure 5. Forest plot of comparison: 1 Thiazides vs active comparators: primary outcomes, outcome: 1.2 Total serious adverse events.



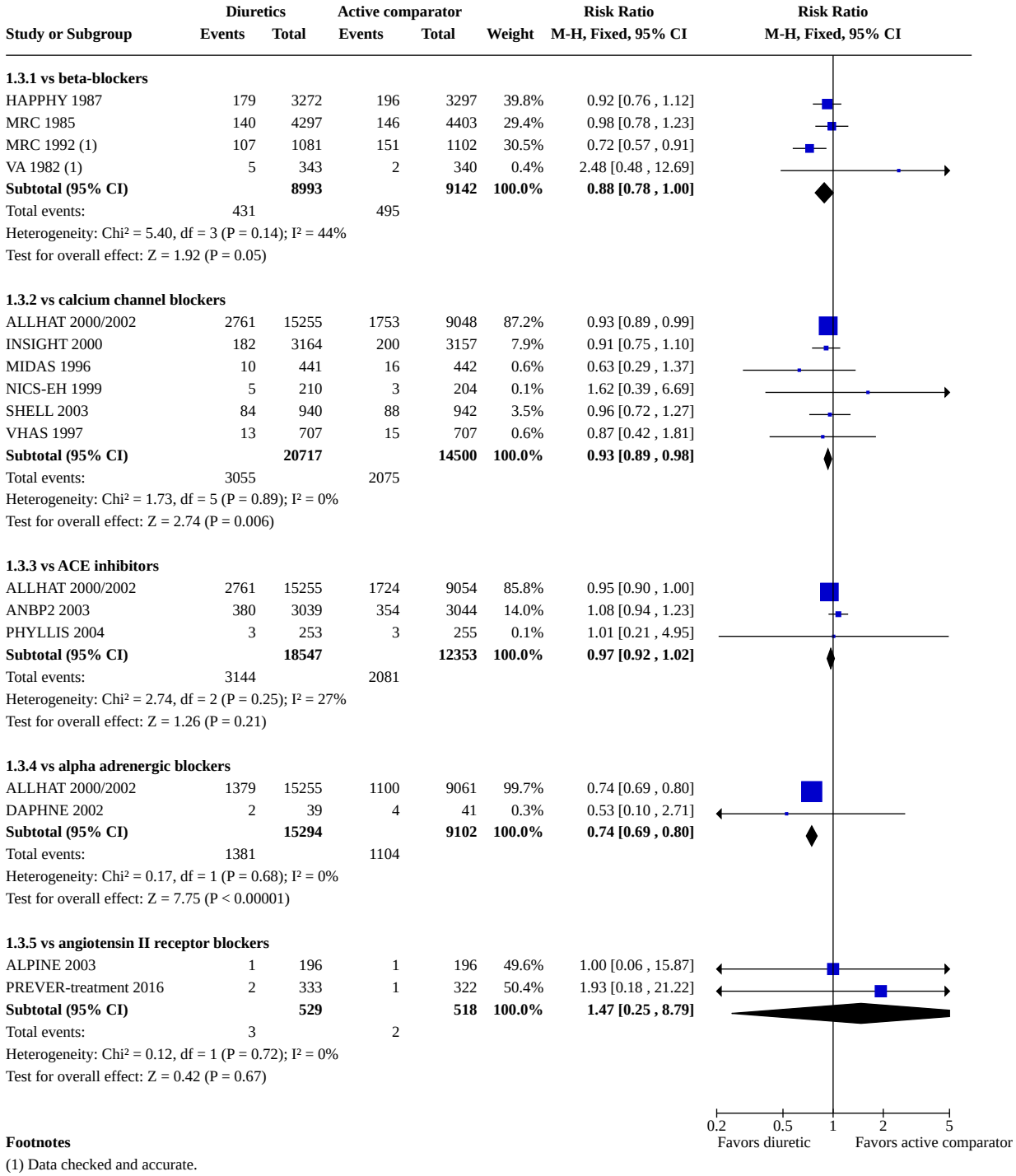
No sensitivity analyses were possible due to the limited number of trials.

Total cardiovascular events

A total of 13 studies reported data for the analysis of total cardiovascular events (Analysis 1.3; Figure 6). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. Four studies compared diuretics to beta-blockers (HAPPHY 1987; MRC 1985; MRC 1992; VA 1982), six compared diuretics to calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; VHAS 1997), three compared diuretics to ACE inhibitors (ALLHAT 2000/2002; ANBP2 2003; PHYLLIS 2004), two compared diuretics to alpha-adrenergic blockers (ALLHAT 2000/2002; DAPHNE 2002), and

two compared diuretics to angiotensin II receptor blockers (ALPINE 2003; PREVER-treatment 2016).

Figure 6. Forest plot of comparison: 1 First-line thiazides vs active comparators: primary outcomes, outcome: 1.3 Total cardiovascular events.



Footnotes

(1) Data checked and accurate.

First-line diuretics likely lower total cardiovascular events slightly compared to beta-blockers (RR 0.88, 95% CI 0.78 to 1.00; Chi^2 = 5.40 (P = 0.14); I^2 = 44%; 4 studies, 18,135 participants; moderate-certainty evidence). First-line diuretics did not change total cardiovascular events as compared with ACE inhibitors (RR 0.97, 95% CI 0.92 to 1.02; Chi^2 = 2.74 (P = 0.25); I^2 = 27 %; 3 studies, 30,900 participants; low-certainty evidence). Diuretics probably reduced total cardiovascular events compared with

calcium channel blockers (RR 0.93, 95% CI 0.89 to 0.98; Chi^2 = 1.73 (P = 0.89); I^2 = 0%; 6 studies, 35,217 participants; moderate-certainty evidence) and alpha-adrenergic blockers (RR 0.74, 95% CI 0.69 to 0.80; Chi^2 = 0.17 (P = 0.68); I^2 = 0%; 2 studies, 24,396 participants; moderate-certainty evidence). In two small trials, first-line diuretics did not change total cardiovascular events compared to angiotensin receptor blockers (RR 1.47, 95% CI 0.25 to 8.79; Chi^2 = 0.12 (P = 0.72); I^2 = 0%; 2 studies, 1047 participants).

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, total cardiovascular events remained numerically less between first-line diuretics and calcium channel blockers (RR 0.91, 95% CI 0.78 to 1.06; 5 studies, 10,914 participants). The lack of effect remained between diuretics and ACE inhibitors (RR 1.07, 95% CI 0.94 to 1.23; 2 studies, 6591 participants). The reductive effect between diuretics and alpha-blockers remained (RR 0.53, 95% CI 0.10 to 2.71; 1 study, 80 participants). This sensitivity analysis was not possible for beta-blockers. When small trials (< 1000 participants in each comparison) were excluded, total cardiovascular events continued to be reduced with diuretics compared to beta-blockers (RR 0.88, 95% CI 0.77 to 1.00; 3 studies, 17,452 participants) and calcium channel blockers (RR 0.93, 95% CI 0.88 to 0.98; 2 studies, 30,624 participants). The lack of effect compared to ACE inhibitors remained (RR 0.97, 95% CI 0.92 to 1.02; 2 studies, 30,392 participants). The reduced effect with diuretics compared to alpha-blockers also remained (RR 0.74, 95% CI 0.69 to 0.80; 1 study, 24,316 participants).

Supplemental drugs

When the trials with no supplemental drugs were deselected, the reduced cardiovascular events between first-line diuretics and beta-blockers were unaffected (RR 0.88, 95% CI 0.77 to 1.00; 3 studies, 17,452 participants), as was the comparison between diuretics and calcium channel blockers (RR 0.93, 95% CI 0.88 to 0.98; 5 studies, 34,803 participants), plus the comparison between diuretics and alpha-blockers (RR 0.74, 95% CI 0.65 to 0.80; 1 study, 24,315 participants). This sensitivity analysis was not possible for ACE inhibitors. When trials where different supplemental drug classes were allowed in each arm were removed, the possible reduction in total cardiovascular events between diuretics and beta-blockers was lost (RR 2.48, 95% CI 0.48 to 12.89; 1 study, 683 participants). The numerical reduction between diuretics and calcium channel blockers remained (RR 0.92, 95% CI 0.72 to 1.18; 4 studies, 4593 participants). The lack of effect between diuretics and ACE inhibitors remained (RR 1.01, 95% CI 0.21 to 4.95; 1 study, 508 participants). The numerical reduction between diuretics and alpha-blockers remained (RR 0.53, 95% CI 0.10 to 2.71; 1 study, 80 participants). The lack of effect between diuretics and angiotensin receptor blockers remained (RR 1.93, 95% CI 0.18 to 21.22; 1 study, 655 participants).

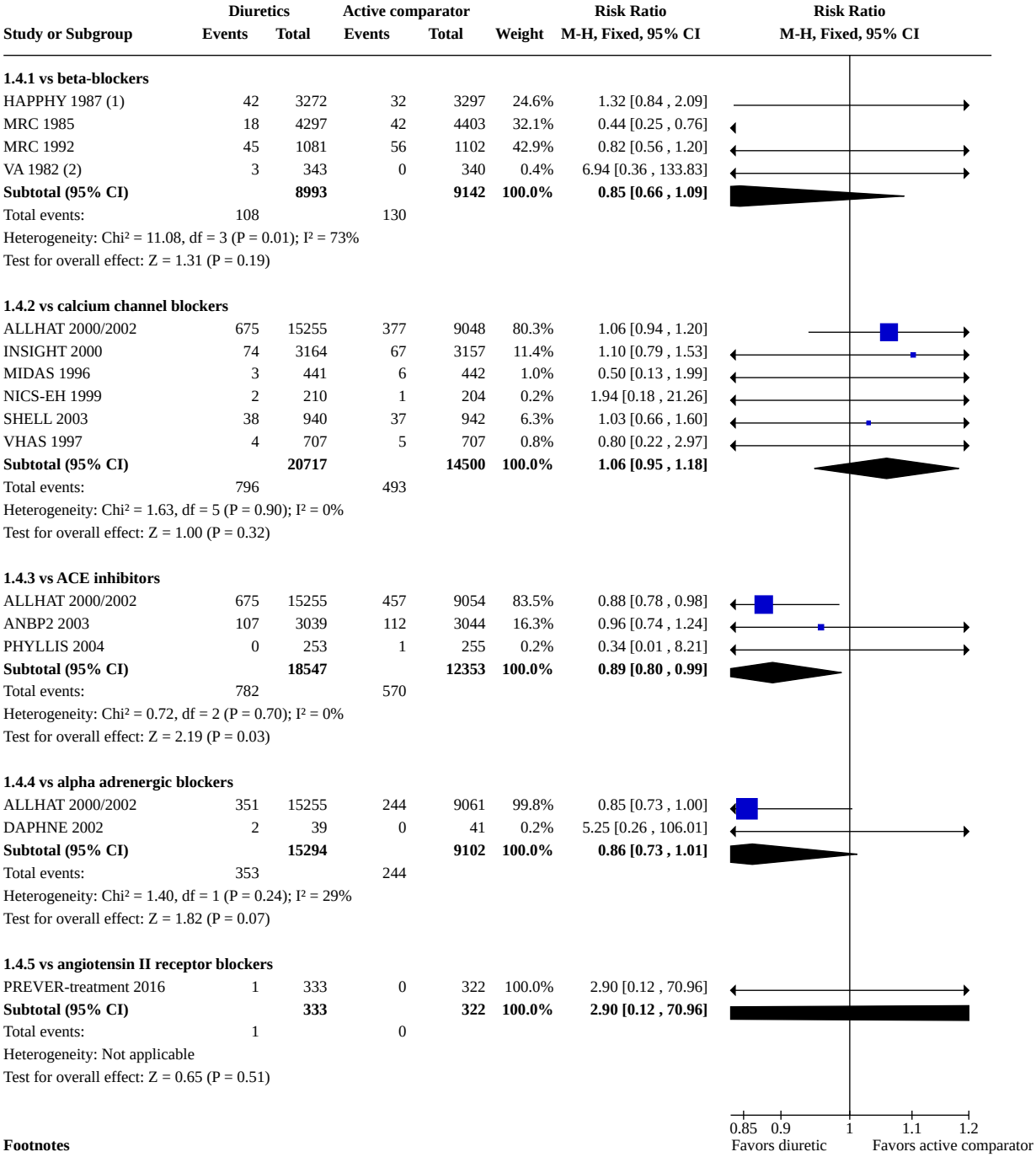
Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected the reduction in total cardiovascular events with thiazides as compared to beta-blockers became more certain (RR 0.72, 95% CI 0.57 to 0.91; 1 study, 2183 participants). There were no trials using high-dose thiazides for the other drug classes.

Total fatal and non-fatal stroke

Total stroke events were reported in 14 studies (Analysis 1.4; Figure 7). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. Four studies compared diuretics to beta-blockers (HAPPHY 1987; MRC 1985; MRC 1992; VA 1982), six compared diuretics to calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; VHAS 1997), three compared diuretics with ACE inhibitors (ALLHAT 2000/2002; ANBP2 2003; PHYLLIS 2004), two compared diuretics with alpha-adrenergic blockers (ALLHAT 2000/2002; DAPHNE 2002), and one compared diuretics with angiotensin II receptor blockers (PREVER-treatment 2016).

Figure 7. Forest plot of comparison: 1 Thiazides vs active comparators: primary outcomes, outcome: 1.4 Total stroke events.



Footnotes

(1) Data checked and accurate

(2) Data checked and accurate.

First-line diuretics likely resulted in little to no difference in stroke as compared with beta-blockers (RR 0.85, 95% CI 0.66 to 1.09; Chi^2 = 11.08 (P = 0.01); I^2 = 73%; 4 studies, 18,135 participants; low-certainty evidence). First-line diuretics probably did not change stroke events compared with calcium channel blockers (RR 1.06, 95% CI 0.95 to 1.18; Chi^2 = 1.63 (P = 0.90); I^2 = 0%; 6 studies, 35,217 participants; moderate-certainty evidence). First-line diuretics reduced total stroke events compared with ACE inhibitors (RR 0.89, 95% CI 0.80 to 0.99; Chi^2 = 0.72 (P = 0.70); I^2 = 0%; 3 studies, 30,900 participants; moderate-certainty evidence), and probably reduced stroke compared to alpha-blockers (RR 0.86, 95% CI 0.73 to 1.01; Chi^2 = 1.48 (P = 0.70); I^2 = 29%; 2 studies, 24,396 participants; moderate-certainty evidence). First-line diuretics did not change stroke in the one small trial compared to angiotensin

receptor blockers (RR 2.90, 95% CI 0.12 to 70.96; 1 study, 655 participants).

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, total stroke remained similar between first-line diuretics and calcium channel blockers (RR 1.04, 95% CI 0.81 to 1.34; 5 studies, 10,914 participants). The certainty of the evidence for a reduction was lost between diuretics and ACE inhibitors (RR 0.95, 95% CI 0.73 to 1.23; 2 studies, 6591 participants). The reduced effect between diuretics and alpha-blockers was lost (RR 5.25, 95% CI 0.26 to 106.01; 1 study, 80 participants). When small trials (< 1000 participants in each comparison) were excluded, total stroke continued to be numerically reduced with diuretics compared to beta-blockers (RR 0.82, 95% CI 0.64 to 1.00; 3 studies, 17,452 participants). The lack of effect on stroke compared to calcium channel blockers remained (RR 1.07, 95% CI 0.95 to 1.20; 2 studies, 30,624 participants). The reduction in stroke compared to ACE inhibitors remained (RR 0.89, 95% CI 0.80 to 0.99; 2 studies, 30,392 participants). The reduced effect with diuretics compared to alpha-blockers also remained (RR 0.85, 95% CI 0.73 to 1.00; 1 study, 24,316 participants).

Supplemental drugs

When the trials with no supplemental drugs were deselected, the reduced stroke events between first-line diuretics and beta-blockers were unaffected (RR 0.82, 95% CI 0.64 to 1.00; 3 studies, 17,452 participants), as was the lack of effect between diuretics and calcium channel blockers (RR 1.06, 95% CI 0.95 to 1.18; 5 studies, 34,803 participants). There were no trials with no supplemental drugs in the ACE inhibitor comparison and the reduction in stroke in the comparison between diuretics and alpha-blockers remained (RR 0.85, 95% CI 0.73 to 1.00; 1 study, 24,316 participants). When trials where different supplemental drug classes were allowed in each arm were removed, the lack of effect on total stroke events remained between diuretics and beta-blockers (RR 6.94, 95% CI 0.36 to 133.83; 1 study, 683 participants), between diuretics and calcium channel blockers (RR 0.96, 95% CI 0.65 to 1.42; 4 studies, 4593 participants), between diuretics and ACE inhibitors (RR 0.34, 95% CI 0.01 to 8.21; 1 study, 508 participants), and between diuretics and alpha-blockers (RR 5.25, 95% CI 0.26 to 106.01; 1 study, 80 participants). This sensitivity analysis was not possible for angiotensin receptor blockers.

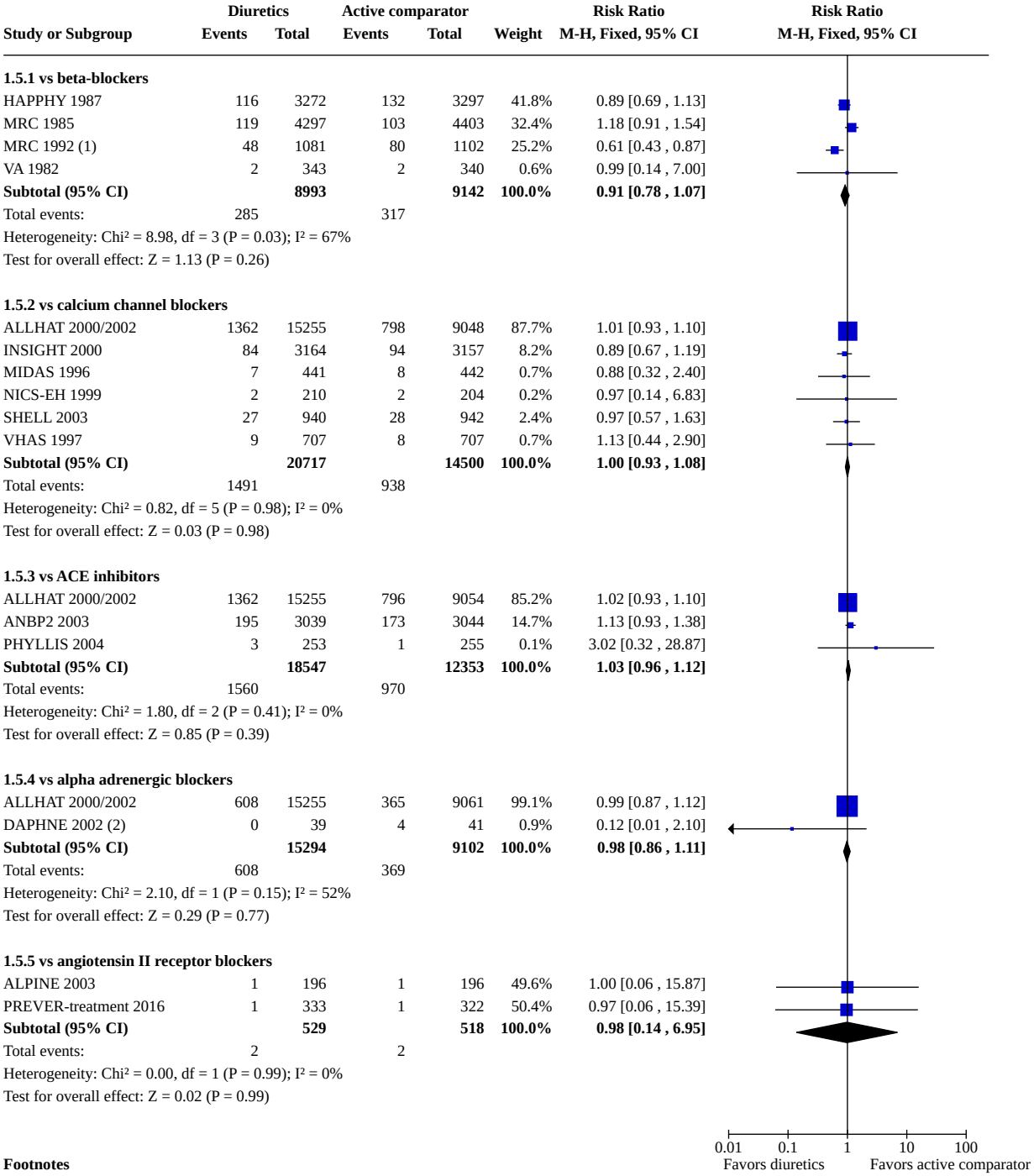
Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected, the numerical reduction in total stroke events with thiazides as compared to beta-blockers was unchanged (RR 0.82, 95% CI 0.56 to 1.20; 1 study, 2183 participants). There were no trials using high-dose thiazides for the other drug classes.

Total coronary heart disease (CHD) events (fatal and non-fatal myocardial infarction plus sudden death)

Fifteen studies were included in the analysis for total CHD events (Analysis 1.5; Figure 8). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals have been shown. This outcome was not different when first-line diuretics were compared to beta-blockers (RR 0.91, 95% CI 0.78 to 1.07; Chi^2 = 8.98, df = 3 (P = 0.03); I^2 = 67%; 4 studies, 18,135 participants; moderate-certainty evidence) (HAPPHY 1987; MRC 1985; MRC 1992; VA 1982), calcium channel blockers (RR 1.00, 95% CI 0.93 to 1.08; Chi^2 = 0.82, df = 5 (P = 0.98); I^2 = 0%; 6 studies, 35,217 participants; moderate-certainty evidence) (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; VHAS 1997), ACE inhibitors (RR 1.03, 95% CI 0.96 to 1.12; Chi^2 = 1.80, df = 2 (P = 0.41); I^2 = 0%; 3 studies, 30,900 participants; low-certainty evidence) (ALLHAT 2000/2002; ANBP2 2003; PHYLLIS 2004), alpha-adrenergic blockers (RR 0.98, 95% CI 0.86 to 1.11; Chi^2 = 2.10, df = 1 (P = 0.15); I^2 = 52%; 2 studies, 24,396 participants; moderate-certainty evidence) (ALLHAT 2000/2002; DAPHNE 2002), and angiotensin II receptor blockers (RR 0.98, 95% CI 0.14 to 6.95; Chi^2 = 0.00, df = 1 (P = 0.99); I^2 = 0%; 2 studies, 1047 participants) (ALPINE 2003; PREVER-treatment 2016).

Figure 8. Forest plot of comparison: 1 Thiazides vs active comparators: primary outcomes, outcome: 1.5 Total coronary events.



Footnotes

(1) MRC 1992 data are correct.

(2) DAPHNE data are correct

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, total CHD events remained not different with diuretics compared to calcium channel blockers (RR 0.92, 95% CI 0.73 to 1.17; 5 studies, 10,914 participants); between diuretics and ACE inhibitors (RR 1.14, 95% CI 0.94 to 1.39; 2 studies, 6591 participants); and between diuretics and alpha-blockers (RR 0.12, 95% CI 0.01 to 2.10; 1 study, 80 participants). When small trials (< 1000 participants in each comparison) were excluded, total CHD events continued to not be different with diuretics compared to beta-blockers (RR

0.91, 95% CI 0.78 to 1.07; 3 studies, 17,452 participants); calcium channel blockers (RR 1.00, 95% CI 0.92 to 1.09; 2 studies, 30,624 participants); ACE inhibitors (RR 1.03, 95% CI 0.96 to 1.11; 2 studies, 30,392 participants); and alpha-blockers (RR 0.99, 95% CI 0.87 to 1.12; 1 study, 24,316 participants).

Supplemental drugs

When the trials with no supplemental drugs were deselected, the lack of effect on CHD events remained between diuretics and beta-blockers (RR 0.91, 95% CI 0.78 to 1.07; 3 studies, 17,452 participants), diuretics and calcium channel blockers (RR 1.00, 95% CI 0.93 to 1.08; 5 studies, 34,803 participants), and diuretics and alpha-blockers (RR 0.99, 95% CI 0.87 to 1.12; 1 study, 24,316 participants). When trials where different supplemental drug classes were allowed in each arm were removed, the lack of effect on total CHD events remained between diuretics and beta-blockers (RR 0.99, 95% CI 0.14 to 7.00; 1 study, 683 participants); diuretics and calcium channel blockers (RR 0.98, 95% CI 0.65 to 1.47; 4 studies, 4593 participants); diuretics and ACE inhibitors (RR 3.02, 95% CI 0.32 to 28.87; 1 study, 508 participants); diuretics and alpha-blockers (RR 0.12, 95% CI 0.01 to 2.10; 1 study, 80 participants), and diuretics and angiotensin receptor blockers (RR 0.97, 95% CI 0.06 to 15.39; 1 study, 655 participants).

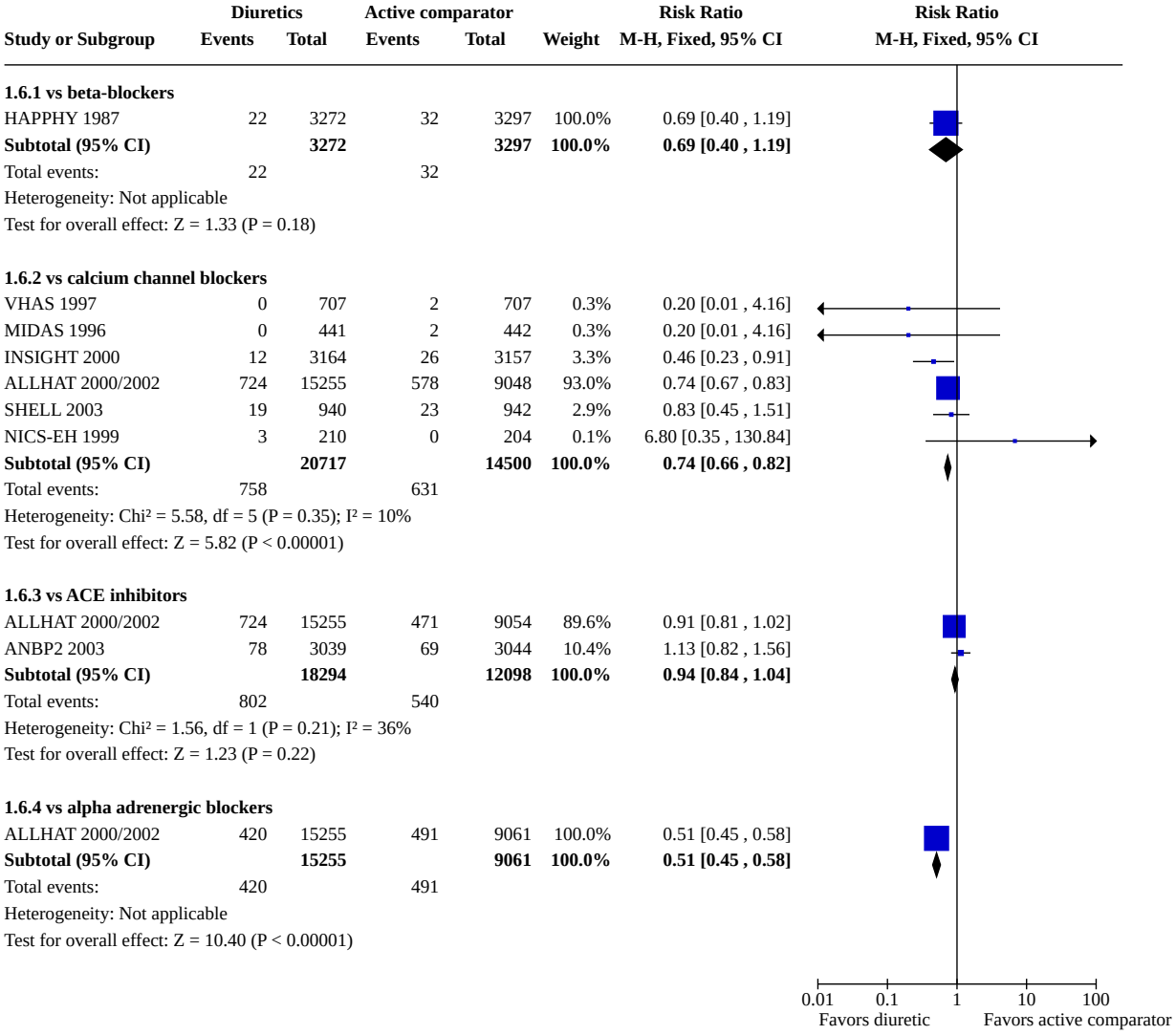
Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected the reduction in total coronary events with thiazides as compared to beta-blockers became more certain (RR 0.61, 95% CI 0.43 to 0.87; 1 study, 2183 participants). There were no trials using high-dose thiazides for the other drug classes.

Total congestive heart failure

In total, eight studies reported data for death or hospitalization due to heart failure (Analysis 1.6; Figure 9). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. One study compared diuretics with beta-blockers (HAPPHY 1987), six studies compared diuretics with calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; VHAS 1997), two studies compared diuretics with ACE inhibitors (ALLHAT 2000/2002; ANBP2 2003), and one study compared diuretics with alpha-adrenergic blockers (ALLHAT 2000/2002).

Figure 9. Forest plot of comparison: 1 Thiazides vs active comparators: primary outcomes, outcome: 1.6 Total congestive heart failure.



First-line diuretics may have resulted in little to no difference in heart failure compared with beta-blockers (RR 0.69, 95% CI 0.40 to 1.19; 1 study, 6569 participants; low-certainty evidence). Diuretics probably decreased heart failure compared to calcium channel blockers (RR 0.74, 95% CI 0.66 to 0.82; Chi^2 = 5.98 (P = 0.35); I^2 = 10%; 6 studies, 35,217 participants; moderate-certainty evidence). Diuretics probably resulted in little to no difference in heart failure compared with ACE inhibitors (RR 0.94, 95% CI 0.84 to 1.04; Chi^2 = 1.56 (P = 0.21); I^2 = 36%; 2 studies, 30,392 participants; moderate-certainty evidence). Diuretics decreased heart failure compared to alpha-adrenergic blockers (RR 0.51, 95% CI 0.45 to 0.58; 1 study, 24,316 participants; moderate-certainty evidence).

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, heart failure continued to be reduced by first-line diuretics compared to calcium channel blockers (RR 0.65, 95% CI 0.43 to 0.99; 5 studies, 10,914 participants). The lack of effect between diuretics and ACE inhibitors remained (RR 1.13, 95% CI 0.82 to 1.56; 1 study, 6083 participants). This analysis was not possible for beta-blockers and alpha-blockers. When small trials (< 1000 participants in each comparison) were excluded, total heart failure continued to be reduced by diuretics compared to calcium channel blockers (RR 0.73, 95% CI 0.66 to 0.81; 2 studies, 30,624 participants). This analysis was not possible for beta-blockers, ACE inhibitors, and alpha-blockers.

Supplemental drugs

When the trials with no supplemental drugs were deselected, the reduced heart failure with diuretics compared to calcium channel blockers remained (RR 0.73, 95% CI 0.66 to 0.81; 5 studies, 34,803 participants). There were no trials with no supplemental drugs in the other comparisons. When trials where different supplemental drug classes were allowed in each arm were removed, the numerical reduction in total CHF events remained between diuretics and calcium channel blockers (RR 0.82, 95% CI

0.45 to 1.42; 4 studies, 4593 participants). This sensitivity analysis was not possible for beta-blockers, ACE inhibitors, and alpha-blockers.

A sensitivity analysis exploring the effect of high-dose thiazides versus beta-blockers was not possible as there was only one trial reporting this outcome.

Withdrawals due to adverse effects

Sixteen studies reported withdrawals due to adverse effects (Analysis 1.7; Figure 10). Five studies compared diuretics to beta-blockers (HAPPHY 1987; Materson 1993; MRC 1985; MRC 1992; VA 1982), seven studies compared diuretics to calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; Materson 1993; MIDAS 1996; NICS-EH 1999; Tresukosol 2005; VHAS 1997), three studies compared diuretics to ACE inhibitors (ALLHAT 2000/2002; Materson 1993; NESTOR 2004), three studies compared diuretics to alpha-adrenergic blockers (ALLHAT 2000/2002; DAPHNE 2002; Materson 1993), two studies compared diuretics to angiotensin II receptor blockers (ALPINE 2003; PREVER-treatment 2016), one study compared a diuretic to a direct renin inhibitor (Schmieder 2009), and one study compared a diuretic to a centrally acting drug, clonidine (Materson 1993).

Figure 10. Forest plot of comparison: 1 First-line thiazides vs active comparators: primary outcomes, outcome: 1.7 Withdrawal due to adverse effects.

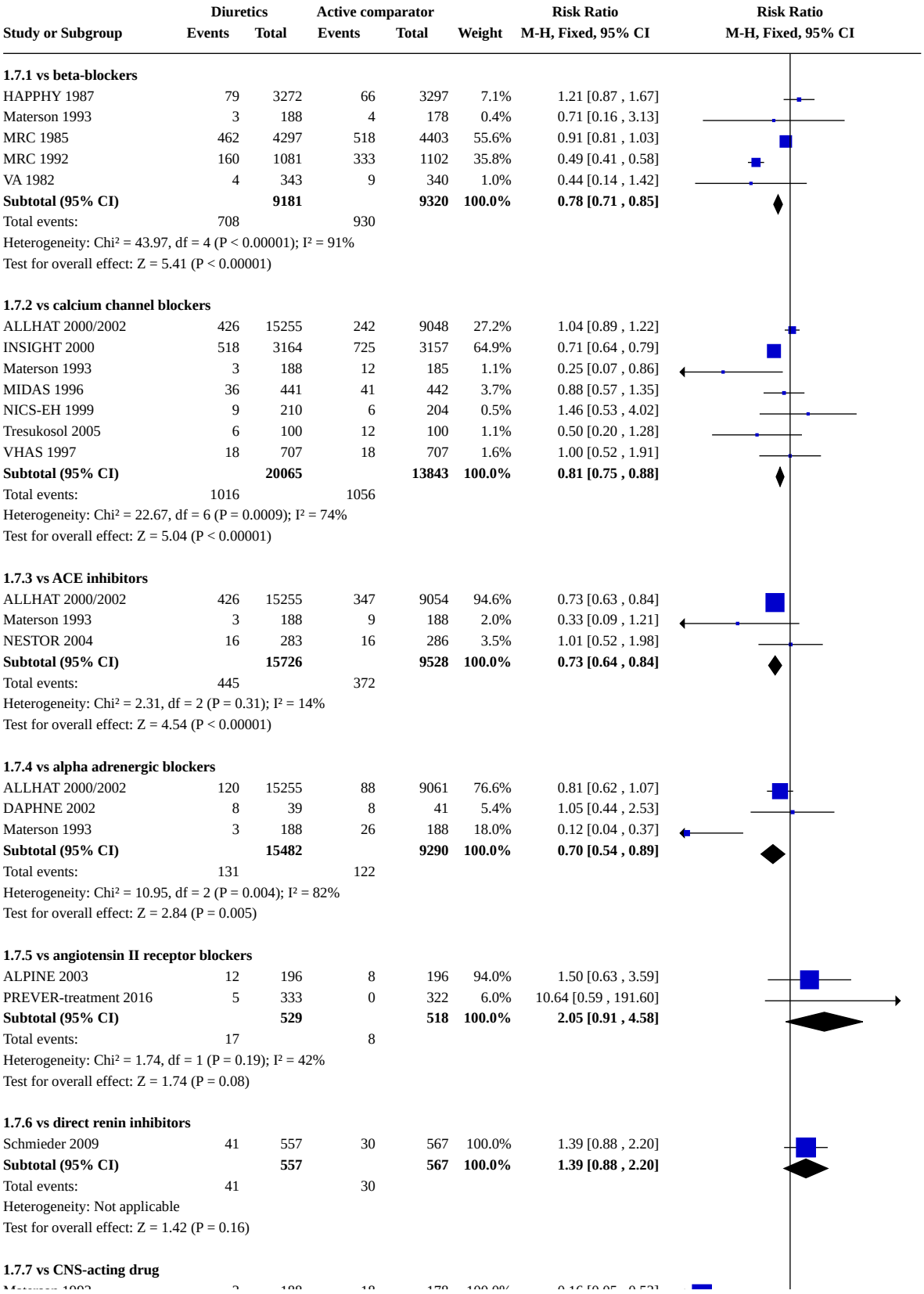
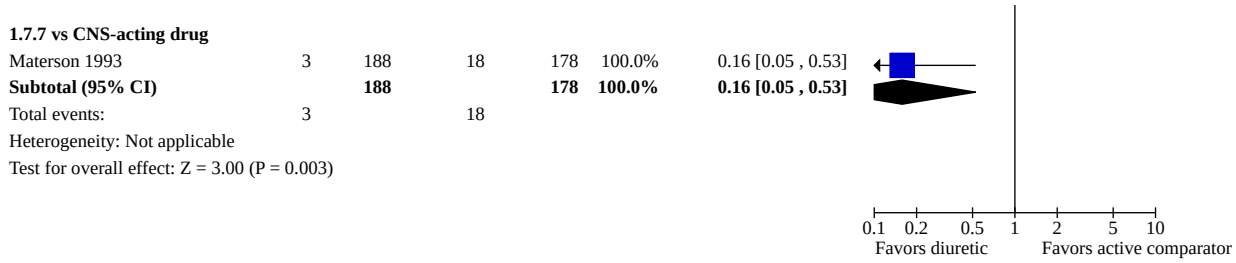


Figure 10. (Continued)



Withdrawals due to adverse effects may have been lowered for first-line diuretics when compared with beta-blockers (RR 0.78. 95% CI 0.71 to 0.85; Chi^2 = 43.97 (P < 0.001); I^2 = 91%; 5 studies, 18,501 participants; moderate-certainty evidence), calcium channel blockers (RR 0.81, 95% CI 0.75 to 0.88; Chi^2 = 22.67 (P < 0.001); I^2 = 74%; 7 studies, 33,908 participants; low-certainty evidence), ACE inhibitors (RR 0.73, 95% CI 0.64 to 0.84; Chi^2 = 2.31 (P = 0.31); I^2 = 14%; 3 studies, 25,254 participants; moderate-certainty evidence), alpha-blockers (RR 0.70, 95% CI 0.54 to 0.89; Chi^2 = 10.95 (P = 0.004); I^2 = 82%; 3 studies, 24,772 participants; low-certainty evidence), and when compared with clonidine, a central nervous system (CNS)-acting drug (RR 0.16, 95% CI 0.05 to 0.53; 1 study, 366 participants). There were no differences in withdrawals due to adverse effects when diuretics were compared with angiotensin II receptor blockers (RR 2.05, 95% CI 0.91 to 4.58; Chi^2 = 1.74 (P = 0.17); I^2 = 42%; 2 studies, 1047 participants) or with direct renin inhibitors (RR 1.39, 95% CI 0.88 to 2.20; 1 study, 1124 participants).

Sensitivity analysis

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, withdrawals due to adverse effects remained reduced by diuretics compared to calcium channel blockers (RR 0.72, 95% CI 0.66 to 0.80; 6 studies, 9605 participants), ACE inhibitors (RR 0.77, 95% CI 0.43 to 1.37; 2 studies, 945 participants), and alpha-blockers (RR 0.33, 95% CI 0.17 to 0.63; 2 studies, 456 participants). This analysis was not possible for beta-blockers. When small trials (< 1000 participants in each comparison) were deselected, withdrawals due to adverse effects continued to be reduced by diuretics compared to beta-blockers (RR 0.78, 95% CI 0.71 to 0.86; 3 studies, 17,452 participants), calcium channel blockers (RR 0.81, 95% CI 0.74 to 0.88; 2 studies, 30,624 participants), ACE inhibitors (RR 0.73, 95% CI 0.63 to 0.84; 1 study, 24,309 participants), and alpha-blockers (RR 0.81, 95% CI 0.62 to 1.07; 1 study, 24,316 participants).

Supplemental drugs

When the trials with no supplemental drugs were deselected, the reduction in withdrawals due to adverse effects remained between first-line diuretics and beta-blockers (RR 0.78, 95% CI 0.71 to 0.86; 3 studies, 17,452 participants), calcium channel blockers (RR 0.81, 95% CI 0.75 to 0.88; 5 studies, 33,121 participants), ACE inhibitors (RR 0.74, 95% CI 0.64 to 0.85; 2 studies, 24,878 participants), and alpha-blockers (RR 0.81, 95% CI 0.62 to 1.07; 1 study, 24,316 participants). When trials where different supplemental drug classes were allowed in each arm were removed, the numerical reduction in withdrawals due to adverse effects remained between diuretics and beta-blockers (RR 0.52, 95% CI 0.21 to 1.31; 2 studies, 1049 participants); calcium channel blockers (RR 0.51, 95% CI 0.60 to 1.09; 5 studies, 3284 participants); ACE inhibitors (RR 0.77, 95% CI 0.43 to 1.37; 2 studies, 945 participants), and alpha-blockers (RR 0.33, 95% CI 0.17 to 0.83; 2 studies, 456 participants). The numerical increase between diuretics and angiotensin receptor blockers remained (RR 10.64, 95% CI 0.54 to 191.60; 1 study, 655 participants). This sensitivity analysis was not possible for renin inhibitors or CNS-active drugs.

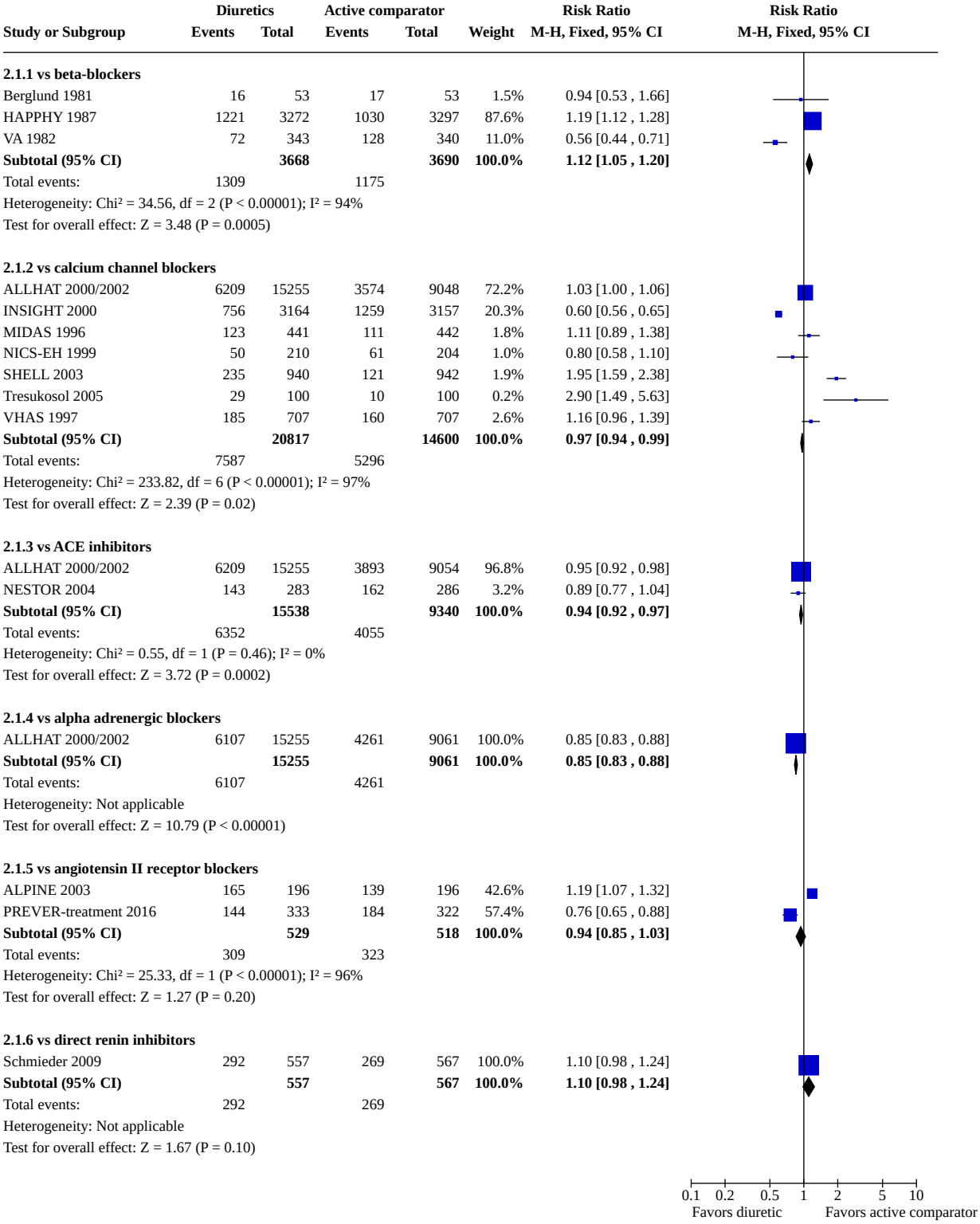
Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected, the reduction in withdrawals due to adverse effects with thiazides as compared to beta-blockers became more prominent (RR 0.49, 95% CI 0.42 to 0.58; 2 studies, 2549 participants). There were no trials using high-dose thiazides for the other drug classes.

Dose titration or add-on therapy

Data for dose titration or add-on therapy were available from 14 studies (Analysis 2.1; Figure 11). The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. Three studies compared diuretics with beta-blockers (Berglund 1981; HAPPHY 1987; VA 1982), seven studies compared diuretics with calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; Tresukosol 2005; VHAS 1997), two studies compared diuretics with ACE inhibitors (ALLHAT 2000/2002; NESTOR 2004), one study compared a diuretic with an alpha-adrenergic blocker (ALLHAT 2000/2002), two studies compared diuretics with angiotensin II receptor blockers (ALPINE 2003; PREVER-treatment 2016), and one study compared a diuretic with a direct renin inhibitor (Schmieder 2009).

Figure 11. Forest plot of comparison: 2 Thiazides vs active comparators: secondary outcomes, outcome: 2.1 Dose titration and addition of second or third drug.



The need for dose titration or add-on therapy was higher for first-line diuretics when compared with beta-blockers (RR 1.12, 95% CI 1.05 to 1.20; Chi^2 = 34.56 (P < 0.00001); I^2 = 94%; 3 studies, 7358 participants). The need for dose titration or add-on therapy was lower for diuretics compared with calcium channel blockers (RR 0.97, 95% CI 0.94 to 0.99; Chi^2 = 233.82 (P < 0.001); I^2 = 97%; 7 studies,

35,417 participants), ACE inhibitors (RR 0.94, 95% CI 0.92 to 0.97; Chi^2 = 0.55 (P = 0.46); I^2 = 0%; 2 studies, 24,878 participants), and alpha-adrenergic blockers (RR 0.85, 95% CI 0.83 to 0.88; 1 study, 24,316 participants). First-line diuretics did not change the need for dose titration or add-on therapy as compared to angiotensin receptor blockers (RR 0.94, 95% CI 0.85 to 1.03; Chi^2 = 25.33 (P < 0.001); I^2 = 96%; 2 studies, 1047 participants) and direct renin inhibitors (RR 1.10, 95% CI 0.98 to 1.24; 1 study, 1124 participants).

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, need for dose titration or add-on therapy remained less with first-line diuretics compared to calcium channel blockers (RR 0.80, 95% CI 0.75 to 0.85; 6 studies, 11,114 participants) and ACE inhibitors (RR 0.89, 95% CI 0.77 to 1.04; 1 study, 305 participants). This sensitivity analysis was not possible for beta-blockers, alpha-blockers, angiotensin receptor blockers, and renin inhibitors. When small trials (< 1000 participants in each comparison) were deselected, the need for dose titration or add-on therapy continued to be greater with diuretics compared to beta-blockers (RR 1.19, 95% CI 1.12 to 1.28; 1 study, 6569 participants). The need for dose titration or add-on therapy continued to be lower for diuretics compared with calcium channel blockers (RR 0.94, 95% CI 0.91 to 0.96; 2 studies, 30,624 participants) and ACE inhibitors (RR 0.95, 95% CI 0.92 to 0.98; 1 study, 24,309 participants). This sensitivity analysis was not possible for alpha-blockers, angiotensin receptor blockers, and renin inhibitors.

Supplemental drugs

When the trials with no supplemental drugs were deselected, the increased need for dose titration or add-on therapy remained between first-line diuretics and beta-blockers (RR 1.19, 95% CI 1.12 to 1.28; 1 study, 6569 participants). This outcome remained reduced between diuretics and calcium channel blockers (RR 0.97, 95% CI 0.94 to 1.00; 6 studies, 35,003 participants). This sensitivity analysis was not possible for ACE inhibitors, alpha-blockers, angiotensin receptor blockers, and renin inhibitors. When trials where different supplemental drug classes were allowed in each arm were removed, the increase in add-on therapy for beta-blockers reversed and became decreased (RR 0.60, 95% CI 0.48 to 0.75; 2 studies, 789 participants). The decrease between diuretics and calcium channel blockers also reversed to an increase (RR 1.34, 95% CI 1.21 to 1.49; 5 studies, 4793 participants). The decrease in add-on therapy remained between diuretics and ACE inhibitors (RR 0.89, 95% CI 0.77 to 1.04; 1 study, 569 participants), and angiotensin receptor blockers (RR 0.76, 95% CI 0.65 to 0.88; 1 study, 655 participants). This sensitivity analysis was not possible for alpha-blockers and renin inhibitors.

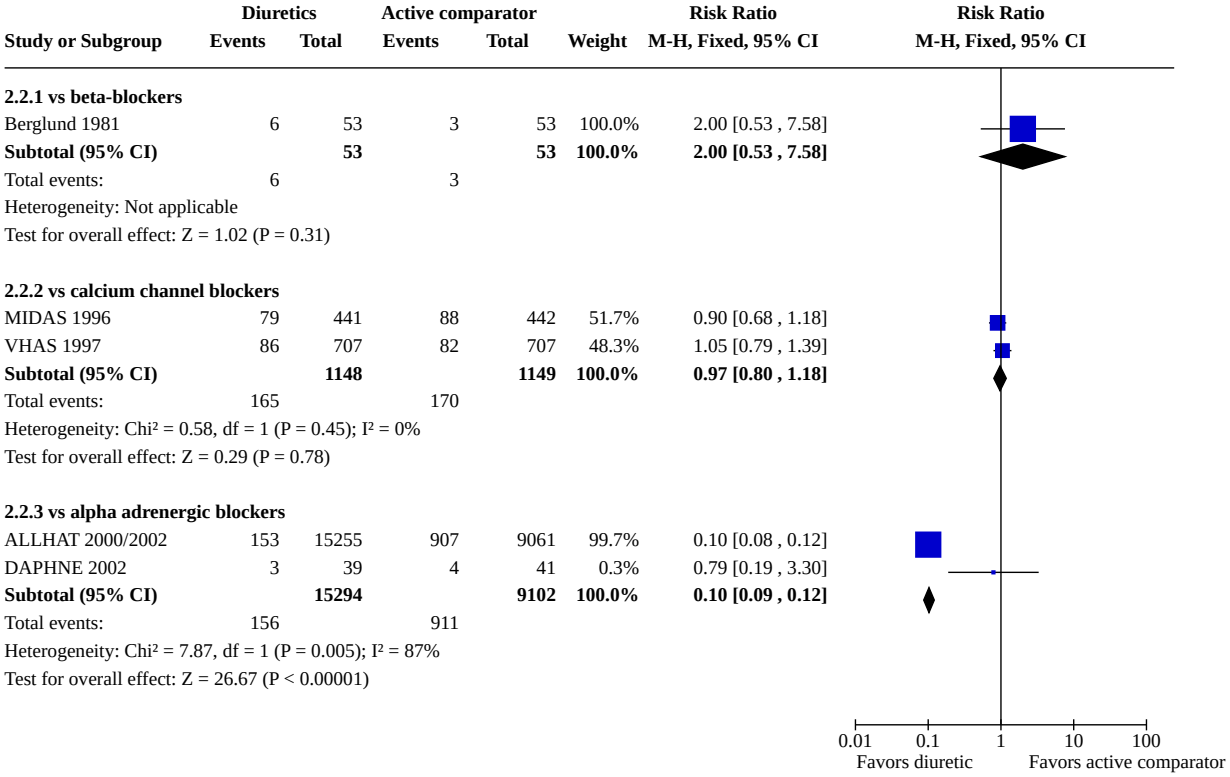
Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected, the increased need for dose titration or add-on therapy with thiazides as compared to beta-blockers was lost (RR 0.94, 95% CI 0.53 to 1.66; 1 study, 106 participants). There were no trials using high-dose thiazides for the other comparisons.

Switching to other antihypertensive therapies

Five studies reported data for participants switching to other antihypertensive therapies (Analysis 2.2; Figure 12). These included one study comparing a diuretic with a beta-blocker (Berglund 1981), two studies comparing diuretics with calcium channel blockers (MIDAS 1996; VHAS 1997), and two studies comparing diuretics with alpha-adrenergic blockers (ALLHAT 2000/2002; DAPHNE 2002).

Figure 12. Forest plot of comparison: 2 Thiazides vs active comparators: secondary outcomes, outcome: 2.2 Switching to other antihypertensive therapies.



First-line diuretics did not affect switching when compared to beta-blockers (RR 2.00, 95% CI 0.53 to 7.58; 1 study, 106 participants) or calcium channel blockers (RR 0.97, 95% CI 0.80 to 1.18; Chi^2 = 0.58 (P = 0.45); I^2 = 0%; 2 studies, 2297 participants). First-line diuretics decreased the need to switch to other antihypertensives when compared with alpha-adrenergic blockers (RR 0.10, 95% CI 0.09 to 0.12; Chi^2 = 7.87 (P = 0.005); I^2 = 87%; 2 studies, 24,396 participants).

Sensitivity analyses

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, the decrease in switching between diuretics and alpha-blockers was lost (RR 0.79, 95% CI 0.19 to 3.30; 1 study, 80 participants). This sensitivity analysis was not possible for beta-blockers, ACE inhibitors, and calcium channel blockers. When small trials (< 1000 participants in each comparison) were deselected, the lack of effect on switching between diuretics and alpha-blockers remained (RR 0.10, 95% CI 0.08 to 0.12; 1 study, 24,316 participants). This sensitivity analysis was not possible for beta-blockers, calcium channel blockers, and ACE inhibitors.

Supplemental drugs

When the trials with no supplemental drugs were deselected, the decreased switching remained between diuretics and alpha-blockers (RR 0.10, 95% CI 0.08 to 0.12; 1 study, 24,316 participants). This sensitivity analysis was not possible for beta-blockers, ACE inhibitors, and calcium channel blockers. When trials where different supplemental drug classes were allowed in each arm were removed, the decrease in switching between diuretics and alpha-blockers was lost (RR 0.79, 95% CI 0.19 to 3.30; 1 study, 80 participants). This sensitivity analysis was not possible for beta-blockers, ACE inhibitors, and calcium channel blockers.

A sensitivity analysis exploring the effect of high-dose thiazides was not possible as there was only one trial reporting this outcome.

Systolic and diastolic blood pressure at one year

Blood pressure data were meta-analyzed from trials that also reported at least one additional outcome of interest (mortality and morbidity); a total of 19 included studies reported 12-month systolic and diastolic blood pressure data (Analysis 2.3; Analysis 2.4; Figure 13; Figure 14).

Figure 13. Forest plot of comparison: 2 Thiazides vs active comparators: secondary outcomes, outcome: 2.3 Systolic blood pressure.

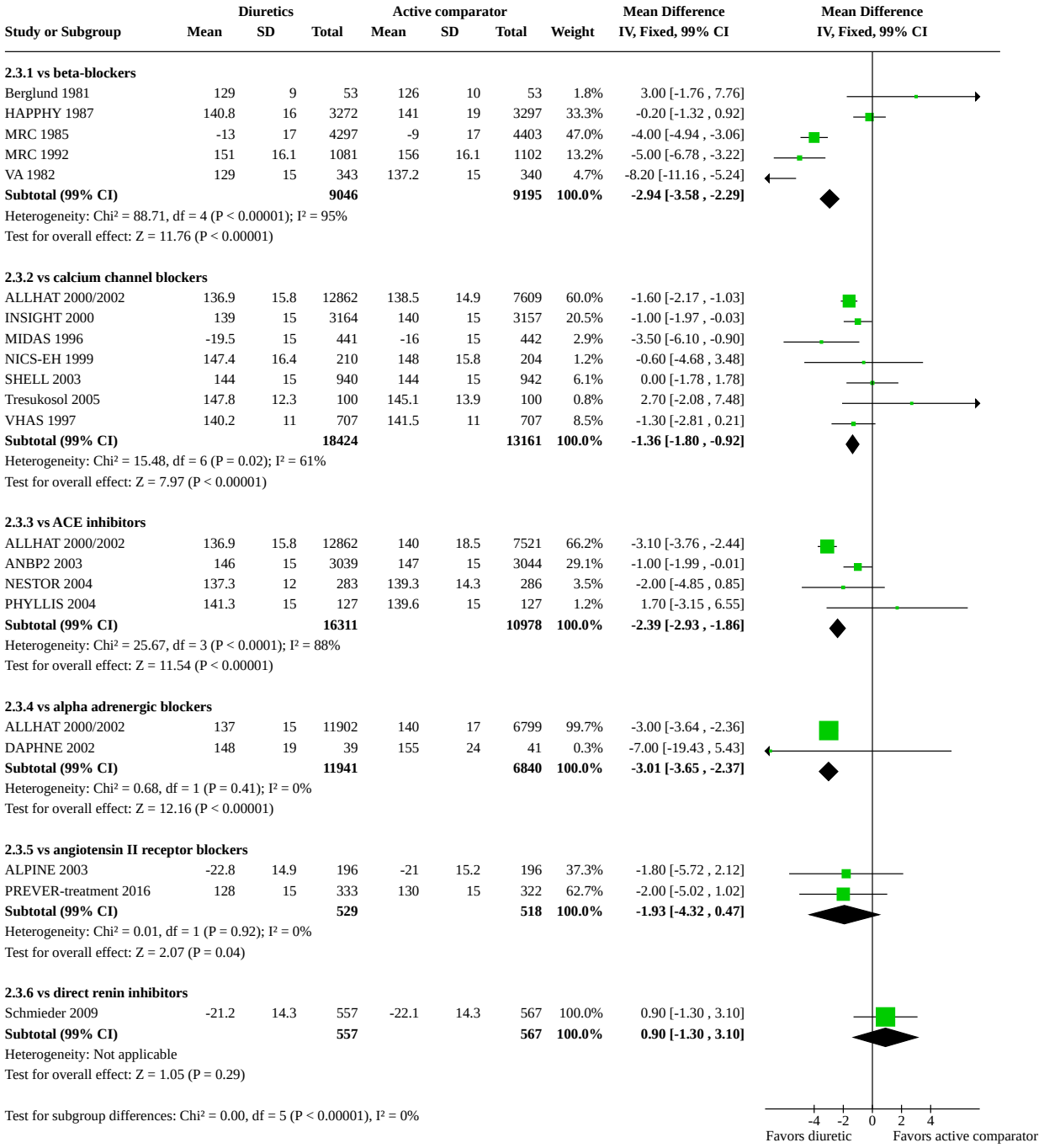
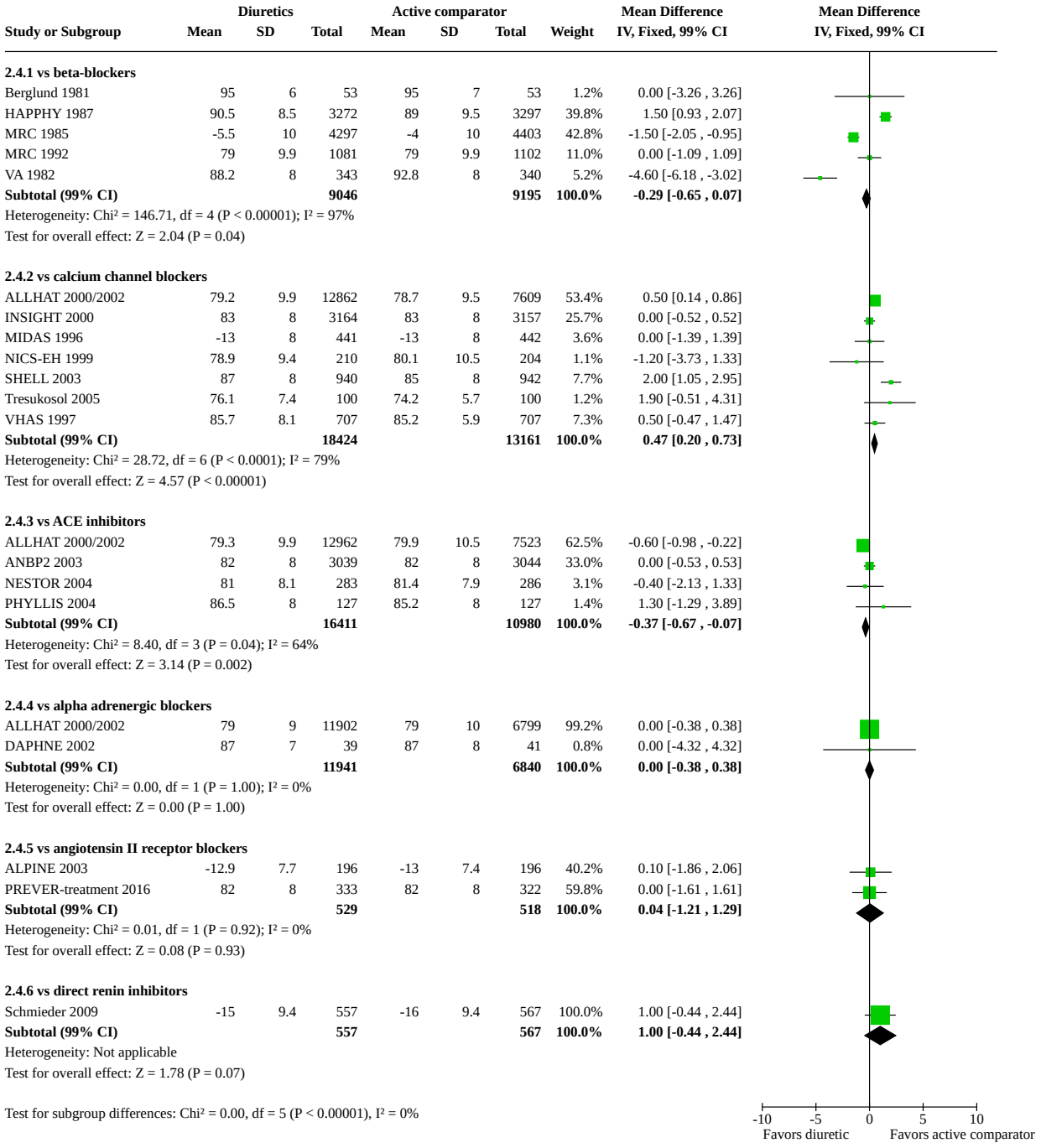


Figure 14. Forest plot of comparison: 2 Thiazides vs active comparators: secondary outcomes, outcome: 2.4 Diastolic blood pressure.



The studies analyzed in this review include five studies comparing diuretics with beta-blockers (Berglund 1981; HAPPHY 1987; MRC 1985; MRC 1992; VA 1982), seven studies comparing diuretics with calcium channel blockers (ALLHAT 2000/2002; INSIGHT 2000; MIDAS 1996; NICS-EH 1999; SHELL 2003; Tresukosol 2005; VHAS 1997), four studies comparing diuretics with ACE inhibitors (ALLHAT 2000/2002; ANBP2 2003; NESTOR 2004; PHYLLIS 2004), two studies comparing diuretics with alpha-adrenergic blockers (ALLHAT 2000/2002; DAPHNE 2002), two studies comparing diuretics with angiotensin II receptor blockers (ALPINE 2003; PREVER-treatment 2016), and one study comparing a diuretic with a direct renin inhibitor (Schmieder 2009).

The ALLHAT trial diuretic group was used for three separate comparisons, therefore only subtotals are shown. In seven of these trials, data were approximated from graphs using imaging software as numerical values were not reported (ANBP2 2003; Berglund 1981; HAPPHY 1987; INSIGHT 2000; PHYLLIS 2004; PREVER-treatment 2016; SHELL 2003). In addition, Tresukosol 2005 reported blood

pressure at 18 months only; this was included as we assumed that this would be approximately equivalent to 12-month data. Six studies had their standard deviation imputed, therefore we have used 99% confidence intervals (ANBP2 2003; INSIGHT 2000; PHYLLIS 2004; PREVER-treatment 2016; SHELL 2003; VA 1982).

First-line diuretics reduced systolic blood pressure more than beta-blockers (mean difference (MD) -2.94, 99% CI -3.58 to -2.29; Chi^2 = 88.71 (P < 0.00001); I^2 = 95%; 5 studies, 18,241 participants); calcium channel blockers (MD -1.36, 99% CI -1.80 to -0.92; Chi^2 = 15.48 (P = 0.02); I^2 = 61%; 7 studies, 31,585 participants); ACE inhibitors (MD -2.39, 99% CI -2.93 to -1.86; Chi^2 = 25.67 (P < 0.0001); I^2 = 88%; 4 studies, 27,289 participants), and alpha-adrenergic blockers (MD -3.01, 99% CI -3.65 to -2.37; Chi^2 = 0.68 (P = 0.41); I^2 = 0%; 2 studies, 18,781 participants) (Analysis 2.3; Figure 13). First-line diuretics numerically decreased systolic blood pressure more than angiotensin II receptor blockers (MD -1.93, 99% CI -4.32 to 0.47; Chi^2 = 0.01 (P = 0.92); I^2 = 0%; 2 studies, 1047 participants). In one trial, diuretics did not change systolic blood pressure compared to a direct renin inhibitor (MD 0.90, 99% CI -1.30 to 3.10; 1 study, 1124 participants).

First-line diuretics did not change diastolic blood pressure compared to beta-blockers (MD -0.29, 99% CI -0.65 to 0.07; Chi^2 = 146.71 (P < 0.00001); I^2 = 97%; 5 studies, 18,241 participants). Diuretics increased diastolic blood pressure as compared to calcium channel blockers (MD 0.47, 99% CI 0.20 to 0.73; Chi^2 = 28.72 (P < 0.0001); I^2 = 79%; 7 studies, 31,585 participants). Diuretics reduced diastolic blood pressure when compared to ACE inhibitors (MD -0.37, 99% CI -0.67 to -0.07; Chi^2 = 8.40 (P = 0.04); I^2 = 64%; 4 studies, 27,391 participants). Diuretics did not change diastolic blood pressure compared with alpha-adrenergic blockers (MD 0.00, 99% CI -0.38 to 0.38; Chi^2 = 0.00 (P = 1.00); I^2 = 0%; 2 studies, 18,781 participants), angiotensin II receptor blockers (MD 0.04, 99% CI -1.21 to 1.29; Chi^2 = 0.01 (P = 0.92); I^2 = 0%; 2 studies, 1047 participants), and direct renin inhibitors (MD 1.00, 99% CI -0.44 to 2.44; 1 study, 1124 participants) (Analysis 2.4; Figure 14).

Sensitivity analysis

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, systolic blood pressure remained reduced by diuretics compared to calcium channel blockers (MD -1.00, 99% CI -1.70 to -0.30; 6 studies, 11,114 participants), ACE inhibitors (MD -1.01, 99% CI -1.93 to -0.09; 3 studies, 6906 participants), and alpha-blockers (MD -7.00, 99% CI -19.43 to 5.43; 1 study, 80 participants). This sensitivity analysis was not possible for beta-blockers, angiotensin receptor blockers, and renin inhibitors. When small trials (< 1000 participants in each comparison) were deselected, systolic blood pressure remained reduced by diuretics compared to beta-blockers (MD -2.79, 99% CI -3.45 to -2.12; 3 studies, 17,452 participants), calcium channel blockers (MD -1.45, 99% CI -1.94 to -0.96; 2 studies, 26,792 participants), ACE inhibitors (MD -2.46, 99% CI -3.01 to -1.91; 2 studies, 26,466 participants), and alpha-blockers (MD -3.00, 99% CI -3.64 to -2.36; 1 study, 18,702 participants). This sensitivity analysis was not possible for angiotensin receptor blockers and renin inhibitors.

Supplemental drugs

When the trials with no supplemental drugs were deselected, systolic blood pressure remained reduced by diuretics compared to beta-blockers (MD -2.79, 99% CI -3.95 to -2.12; 3 studies, 17,454 participants), calcium channel blockers (MD -1.37, 99% CI -1.81 to -0.93; 6 studies, 31,171 participants), and alpha-blockers (MD -3.00, 99% CI -3.64 to -2.36; 1 study, 18,701 participants). This sensitivity analysis was not possible for ACE inhibitors, angiotensin receptor blockers, and renin inhibitors. When trials where different supplemental drug classes were allowed in each arm were removed, systolic blood pressure remained reduced by diuretics compared to beta-blockers (MD -5.08, 99% CI -7.59 to -2.57; 2 studies, 789 participants), calcium channel blockers (MD -1.00, 99% CI -2.00 to -0.00; 5 studies, 4793 participants), ACE inhibitors (MD -1.05, 99% CI -3.51 to 1.41; 2 studies, 823 participants), alpha-blockers (MD -7.00, 99% CI -19.43 to 5.43; 1 study, 80 participants), and angiotensin receptor blockers (MD -2.00, 99% CI -5.02 to 1.02; 1 study, 655 participants). This sensitivity analysis was not possible for renin inhibitors.

Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected the reduction in systolic blood pressure with thiazides as compared to beta-blockers remained (MD -4.02, 99% CI -5.69 to -2.36; 2 studies, 2289 participants). There were no trials using high-dose thiazides for the other drug classes.

Small versus large trials

When the largest trial, ALLHAT 2000/2002, was deselected, diastolic blood pressure remained increased slightly by diuretics compared to calcium channel blockers (MD 0.43, 99% CI 0.04 to 0.81; 6 studies, 11,114 participants). The reduction as compared to ACE inhibitors was lost (MD 0.01, 99% CI -0.48 to 0.51; 3 studies, 6906 participants). The lack of effect compared to alpha-blockers remained (MD 0.00, 99% CI -4.32 to 4.32; 1 study, 80 participants). This sensitivity analysis was not possible for beta-blockers, angiotensin receptor blockers, and renin inhibitors. When small trials (< 1000 participants in each comparison) were deselected, diastolic blood pressure remained unaffected by diuretics compared to beta-blockers (MD -0.05, 99% CI -0.42 to 0.33; 3 studies, 17,452 participants). The increase compared to calcium channel blockers remained (MD 0.34, 99% CI 0.04 to 0.63; 2 studies, 26,792 participants). The reduction as compared to ACE inhibitors persisted (MD -0.39, 99% CI -0.70 to -0.08; 2 studies, 26,568 participants). The lack of effect compared to alpha-blockers remained (MD 0.00, 99% CI -0.38 to 0.38; 1 study, 18,701 participants). This sensitivity analysis was not possible for angiotensin receptor blockers and renin inhibitors.

Supplemental drugs

When the trials with no supplemental drugs were deselected, diastolic blood pressure remained unaffected by diuretics compared to beta-blockers (MD -0.05, 99% CI -0.42 to 0.33; 3 studies, 17,452 participants). The increase compared to calcium channel blockers remained (MD 0.48, 99% CI 0.22 to 0.75; 6 studies, 31,171 participants). The lack of effect compared to alpha-blockers remained (MD 0.00, 99% CI -0.38 to 0.38; 1 study, 18,701 participants). This sensitivity analysis was not possible for ACE inhibitors, angiotensin receptor blockers, and renin inhibitors. When trials where different supplemental drug classes were allowed in each arm were removed, diastolic blood pressure

became reduced by diuretics compared to beta-blockers (MD -3.73, 99% CI -5.15 to -2.31; 2 studies, 789 participants). The increase in diastolic blood pressure remained with diuretics compared to calcium channel blockers (MD 0.96, 99% CI 0.38 to 1.53; 5 studies, 4793 participants). The lack of effect remained for diuretics compared to ACE inhibitors (MD 0.12, 99% CI -1.31 to 1.56; 2 studies, 823 participants), alpha-blockers (MD 0.00, 99% CI -4.32 to 4.32; 1 study, 80 participants), and angiotensin receptor blockers (MD 0.00, 99% CI -1.61 to 1.61; 1 study, 655 participants). This sensitivity analysis was not possible for renin inhibitors.

Dosage of thiazides

In an exploratory sensitivity analysis where trials using high-dose thiazides were deselected, the lack of effect on diastolic blood pressure with thiazides as compared to beta-blockers remained (MD 0.00, 99% CI -1.04 to 1.04; 2 studies, 2289 participants). There were no trials using high-dose thiazides for the other drug classes.

DISCUSSION

Summary of main results

The justification for the use of antihypertensive drugs in people with elevated blood pressure primarily comes from placebo/no treatment controlled trials in people aged 60 and over with moderate to severe elevations of blood pressure (> 160/100 mmHg) (Musini 2019). In that setting antihypertensive drugs reduce mortality and total cardiovascular events. In people aged 18 to 59 with mild to moderate elevations of blood pressure, evidence has only been found for a reduction in the incidence of stroke (low-certainty) (Musini 2017). In people of all ages who are healthy except for mild elevations of blood pressure (140 to 159/90 to 99 mmHg) the evidence remains uncertain as to whether the benefits of drug therapy outweigh the harms (Diao 2012; Sheppard 2018; Sundström 2015). This uncertainty of evidence and conservative approach is supported by the recently updated review assessing blood pressure targets (Arguedas 2020). This target review demonstrates that the benefits of the intervention, trying to achieve a lower blood pressure target as compared to a standard target (≤ 140/90 mmHg), do not outweigh the harms associated with that intervention.

In clinical settings where antihypertensive therapy is indicated, it is important to know what drug class is the best to begin with. This review addresses that question and summary of findings tables are provided for individual drug class comparisons between thiazides and beta-blockers (Summary of findings 1), calcium channel blockers (Summary of findings 2), ACE inhibitors (Summary of findings 3), and alpha-blockers (Summary of findings 4). For these four comparisons, the data were sufficient to justify including them in the table. The amount of data for all comparisons with angiotensin receptor blockers, direct renin inhibitors, and centrally acting drugs was insufficient to justify including them in a summary of findings table.

When a clinician is deciding what drug to start for a patient with hypertension, it is most appropriate to look at the totality of data for each comparison. The comparison of diuretics to beta-blockers is based on six RCTs, all studying a thiazide diuretic with fewer than 20,000 participants. As can be seen in Summary of findings 1, compared to beta-blockers, diuretics likely reduce total cardiovascular events (absolute risk reduction (ARR) 0.6%; moderate-certainty evidence) and withdrawals due to adverse effects (ARR 2.2%; moderate-certainty evidence). For secondary outcomes, the proportion of participants requiring add-on therapy was greater for diuretics than for beta-blockers but it is worth noting that this finding was based on only one trial (HAPPHY 1987), which used a high-dose thiazide and was judged to have a high risk of bias due to lack of blinding and industry involvement. In the two smaller trials where data were available, the opposite was true. Diuretics requiring more add-on therapy does not fit with another major advantage of diuretics; at one-year diuretics lowered systolic blood pressure by 2.6 mmHg more than beta-blockers. The effect on diastolic blood pressure was similar for the two classes of drugs. In sensitivity analyses, these findings were insensitive to the size of trials and to supplemental drugs

In almost all the trials included in this review, the diuretic was a low-dose thiazide. This is important because in the review comparing first-line drug classes with placebo or no treatment (Wright 2018), low-dose thiazides are defined and the evidence was consistent with the fact that high-dose thiazides were not as good at reducing coronary heart disease events as low-dose thiazides. The three trials where high-dose thiazides were used were older trials comparing thiazides with beta-blockers: HAPPHY 1987, MRC 1985, and VA 1982. In an exploratory sensitivity analysis where the high-dose thiazide trials were deselected (see Effects of interventions), diuretics, as compared to beta-blockers, reduced total mortality (RR 0.82, 95% CI 0.66 to 1.01), total cardiovascular events (RR 0.72, 95% CI 0.57 to 0.91), and total CHD (RR 0.61, 95% CI 0.43 to 0.87). In addition, the advantage of low-dose thiazides in terms of withdrawals due to adverse effects became more prominent (RR 0.49, 95% CI 0.41 to 0.58). Thus, the totality of evidence comparing diuretics and beta-blockers favors a low-dose thiazide for hypertension, unless there is another indication for a beta-blocker or a contraindication for a thiazide.

The comparison of first-line diuretics with first-line calcium channel blockers is based on eight RCTs with over 35,000 participants. Most of the data for this comparison used the thiazide-like diuretic chlorthalidone compared to a dihydropyridine calcium channel blocker. As can be seen in Summary of findings 2, diuretics are likely not different from calcium channel blockers for total mortality, total stroke, and total coronary heart disease. However, diuretics as compared to calcium channel blockers likely decreased heart failure and total cardiovascular events (moderate-certainty). Diuretics may reduce withdrawals due to adverse effects as compared to calcium channel blockers (low-certainty). The decrease in total cardiovascular events is completely explained by the decrease in congestive heart failure. This effect was insensitive to the size of trials and the use of supplemental drugs. It was also insensitive to whether the diuretic was chlorthalidone or a thiazide. This means that choosing a diuretic over a calcium channel blocker would likely prevent 1.2% of patients from experiencing death or hospitalization for heart failure. In addition, it might prevent 1.4% of patients from withdrawing due to adverse effects. For secondary outcomes, diuretics had an advantage over calcium channel blockers in requiring less add-on therapy but the data were heterogeneous. At one year, diuretics also lowered systolic blood pressure on average by 1.3 mmHg more than calcium channel blockers and calcium channel blockers lowered diastolic blood pressure on average by 0.5 mmHg more than diuretics. Thiazides likely prevent hospitalizations and death from heart failure compared to calcium channel blockers and are possibly better tolerated, therefore they are the preferred choice. The use

of calcium channel blockers first-line for hypertension undoubtedly leads to hospitalizations for heart failure. It is important for healthcare workers to recognize this as a potentially preventable cause of heart failure.

The comparison of first-line diuretics with first-line ACE inhibitors is based on five RCTs and over 30,000 participants. As can be seen in Summary of findings 3, diuretics are likely not different from ACE inhibitors for total mortality, total cardiovascular events, total coronary heart disease, and total congestive heart failure. However, diuretics likely decrease total stroke events (ARR 0.6%; moderate-certainty) and withdrawals due to adverse effects (ARR 1.0%; moderate-certainty). This means that choosing a diuretic over an ACE inhibitor likely would prevent 0.6% of patients from experiencing a stroke. It is important to appreciate that sensitivity analyses showed that this finding were dependent on the ALLHAT 2000/2002 trial. Prescribing a thiazide instead of an ACE inhibitor would likely prevent 1% of patients from withdrawing due to adverse effects (number needed to treat for an additional beneficial outcome (NNTB) 100). For secondary outcomes, diuretics had an advantage over ACE inhibitors in requiring less add-on therapy. In keeping with this, at one year, diuretics lowered systolic blood pressure on average by 2.5 mmHg more than ACE inhibitors and lowered diastolic blood pressure on average by 0.4 mmHg more than ACE inhibitors. Thiazides are thus a preferred first-line choice over ACE inhibitors. It is possible that thiazide-related reduction of stroke as compared to ACE inhibitors may be due to the greater reduction in systolic and diastolic blood pressure.

The comparison of first-line diuretics with first-line alpha-blockers is based on three RCTs with fewer than 25,000 participants and a mean follow-up of 3.3 years. The shorter follow-up duration was because the alpha-blocker arm of the ALLHAT trial was stopped early when it became evident that doxazosin was inferior to the diuretic, chlorthalidone. As can be seen in Summary of findings 4, diuretics were likely not different from alpha-blockers for total mortality and total coronary heart disease. However, diuretics likely decrease total cardiovascular events, total stroke, and total congestive heart failure compared to alpha-blockers (moderate-certainty). In addition, diuretics may reduce withdrawals due to adverse effects (low-certainty). This means that choosing a thiazide over an alpha-blocker would likely prevent 3.1% of patients from having an adverse cardiovascular event. This benefit was mostly due to a 2.6% reduction in total heart failure events. Withdrawals due to adverse effects may be 0.4% less for a diuretic. For secondary outcomes, thiazides had an advantage over alpha-blockers in requiring less add-on therapy, less switching, and by reducing systolic blood pressure at one year by 3 mmHg more than alpha-blockers. The effect on diastolic blood pressure was not different. Thus despite having less head-to-head data, thiazides are a preferred first-line choice over alpha-blockers.

Only two small RCTs compared diuretics to angiotensin receptor blockers and only one RCT compared a diuretic to a direct renin inhibitor. In these trials, diuretics did not differ for mortality, total cardiovascular events, stroke, CHD, withdrawals due to adverse effects, and systolic and diastolic blood pressure compared to the comparators. In one RCT that compared a diuretic to a centrally acting drug the diuretic reduced withdrawals due to adverse effects by 8.5% at one year. None of the other outcomes were reported for this comparison.

Blood pressure data were available at one year for 17 of the 20 trials. These trials are useful for comparing the blood pressure-lowering effect between diuretics and the other classes. These data should not be used as an estimate of the magnitude of blood pressure lowering for thiazides or the other classes of drugs because these studies allowed dose titration and addition of other drugs. The largest included trial showed that the first-line thiazide-like diuretic lowered systolic blood pressure at one year more than ACE inhibitors, calcium channel blockers, and alpha-blockers (ALLHAT 2000/2002). This effect was confirmed when ALLHAT 2000/2002 was removed from the overall analysis. These findings are based on a large number of trials and were unaffected by sensitivity analyses testing the effect of small versus large trials or the use of supplementary drugs. Also, these findings are consistent with the Cochrane Review of the blood pressure-lowering effect of thiazide diuretics, which as a class lower systolic blood pressure more than diastolic blood pressure and as a class have the greatest effect to lower pulse pressure (Musini 2014). This greater ability of thiazides to lower systolic blood pressure could have advantages in large population studies and could be an explanation for the fact that in this review diuretics reduced some morbidity outcomes more than other classes of drugs.

Overall completeness and applicability of evidence

The search strategy identified all relevant trials up until March 2021. A top-up search of the Cochrane Hypertension Specialized Register to July 2022 retrieved 51 unique records, but no additional included studies. Overall, 16 of the 20 studies reported the primary outcome of total mortality. Unfortunately only three smaller studies reported total serious adverse events. The other most important outcome was total cardiovascular events and that was reported in 15 studies. These were in general lower with first-line diuretics suggesting that they are the best choice for most patients with hypertension. The populations studied in these reviews were mostly older male and female patients (aged 50 to 75) with multiple co-morbidities. In fact, in the largest trial with the greatest impact on the results, the ALLHAT 2000/2002 trial, over 40% of the patients had type 2 diabetes at baseline. Therefore, the results of this review are applicable to a wide spectrum of hypertensive patients including those with type 2 diabetes. This is important as patients with diabetes are often preferentially treated with drugs inhibiting the renin-angiotensin system. The results are also primarily relevant to first-line thiazides and thiazide-like drugs starting with low doses. Only three trials started with high-dose thiazides.

We did not find any trials studying first-line loop diuretics and thus our review findings cannot be generalized to any diuretic. The fact that we did not find any trials studying loop diuretics is not surprising as loop diuretics are not currently considered first-line drugs for the treatment of hypertension in major clinical practice guidelines (Whelton 2018; Williams 2018). In our published protocol, loop diuretics were included as we were under the assumption that they might lower blood pressure in a similar fashion to thiazides and thiazide-like drugs (Musini 2014; Musini 2015). However, during the review development process, the field of hypertension management has evolved. For our next update, we will revise our approach and exclude loop diuretics from the first-line diuretics to be studied.

Quality of the evidence

We have used a modified version of the Cochrane risk of bias tool by adding two domains under the 'Other' category. These two domains were the use of supplemental drugs and industry sponsorship. When comparing first-line antihypertensive drugs the purest design would be to not allow any supplemental drugs. This was the case for five smaller studies in this review (Berglund 1981; DAPHNE 2002; Materson 1993; NICS-EH 1999; VA 1982). However, common practice treatment of hypertension uses a stepped-care approach. In this review, 15 trials allowed supplemental drugs. We have judged that trials where different supplemental drug classes or doses were allowed in the different arms were at high risk of bias. For future updates, we will explore the application of version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2) for assessing risk of bias in included studies (Higgins 2021).

The largest study, with three comparator arms, was different from the other trials in allowing people on antihypertensive therapy at baseline to be enrolled (ALLHAT 2000/2002). This could create a legacy effect, although that is unlikely in that the trial lasted five years. Where possible we have deselected ALLHAT 2000/2002 in sensitivity analyses and the findings were insensitive to removing the trial. In other words the findings of ALLHAT were similar to the other trials.

In addition, the largest study with three comparator arms (ALLHAT 2000/2002) and two other large studies (MRC 1985; MRC 1992) were primarily funded by government sources and potentially less biased. Many of the other studies were designed and conducted with industry sponsorship, including some larger studies; in these studies, the industry sponsorship favored the comparator drug (ANBP2 2003; HAPPHY 1987; INSIGHT 2000; SHELL 2003) and thus were potentially biased against the diuretic arm. Only one small study favoring the thiazide arm was sponsored by a company (NESTOR 2004).

We considered five domains in grading the overall certainty of evidence: risk of bias or limitations in study design and implementation, unexplained heterogeneity or inconsistency of results, imprecision in results, indirectness of evidence, and high probability of publication bias. The majority of studies had a high risk of bias for funding, addition of supplemental drugs, performance bias due to lack of blinding, or attrition bias due to high losses to follow-up. We have downgraded most of the outcomes due to these sources of bias and thus none of the outcomes are judged to be based on high-certainty evidence. It should be noted that we have not considered the direction of bias in this judgment. Most of the funding bias was against the diuretic arm; thus it is possible that the true benefits of diuretics are larger and some of the findings should be judged as high-certainty. We downgraded a few outcomes (mostly withdrawals due to adverse effects) due to inconsistency of the results. We downgraded one outcome due to imprecision: heart failure, for diuretics as compared to beta-blockers. No outcomes were downgraded due to indirectness as we judged the populations studied to be a good reflection of the population being treated for hypertension in the real-world setting. There was no evidence of publication bias and thus we did not downgrade the results for that domain. We assessed all comparisons for the main review outcomes as having moderate or low certainty (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4).

As discussed above, the heterogeneity in the beta-blocker data was eliminated by deselecting the trials where the thiazide doses were high. In addition to explaining the heterogeneity, it clarified that low-dose thiazides reduced total cardiovascular events, total coronary heart disease events, and withdrawals due to adverse effects as compared to beta-blockers. The heterogeneity in withdrawals due to adverse effects with calcium channel blockers was eliminated by deselecting ALLHAT 2000/2002 and Tresukosol 2005 where amlodipine was the calcium channel blocker. This would be worth exploring in more detail as withdrawals due to adverse effects were not a prespecified outcome in ALLHAT 2000/2002.

Potential biases in the review process

We made an assumption that all studies published prior to 1998 had been adequately screened and captured in Wright 1999, and literature searches were only conducted for the years including 1998 and onward. It remains possible that relevant studies published prior to these years may not have been identified in the previous systematic review. This potential was minimized by checking included studies against those of other similar systematic reviews (Chen 2018; Psaty 2003; Wiysonge 2017; Zhu 2021), and thus it is considered to be highly unlikely.

Studies were only included if they reported one of the primary outcomes of interest. Several studies that only reported changes in blood pressure were not assessed, therefore the results for changes in systolic and diastolic blood pressure do not include all studies that otherwise met the inclusion criteria.

We dealt with unit of analysis issues by not combining outcomes from the two multi-arm trials (ALLHAT 2000/2002; Materson 1993). Another potential unit of analysis issue is that despite attempting to only include data from people with at least one event for each of the outcomes there may have been trials where events were reported. It is possible that for some outcomes we overcounted by including events rather than people with one event. This would be unlikely to cause bias as the increased numerator would have occurred in both groups.

The review identified three studies that only reported pooled data from patients treated with diuretics and other drug classes (CONVINCE 2003; Neaton 1993; STOP-Hypertension-2 1999). We sought unpublished data specific to the drug classes from these studies but data were not provided by the authors; if such data are obtained in the future, these studies will be included in the meta-analysis.

Agreements and disagreements with other studies or reviews

Differences in mortality and cardiovascular outcomes between diuretics and other classes of antihypertensives have been assessed in other similar systematic reviews (Chen 2018; Psaty 2003; Thomopoulos 2015; Wiysonge 2017; Wright 1999; Zhu 2021). These other reviews have not taken the approach we have used here of looking at the totality of evidence for first-line diuretics versus each of the other drug classes individually. Our findings favoring diuretics over beta-blockers use the same trial data as Wiysonge 2017, though in that review they did not include withdrawals due to adverse effects as a primary outcome as we have. We have shown that diuretics and specifically thiazides

tend to have lower adverse cardiovascular outcomes overall and reduce withdrawals due to adverse effects. Thus they are better tolerated as well as reducing systolic blood pressure more than beta-blockers.

Our review showing that diuretics reduce congestive heart failure events compared with calcium channel blockers is concordant with a network meta-analysis (Psaty 2003), as well as two more recent systematic reviews (Thomopoulos 2015; Zhu 2021). We have shown that diuretics also reduce withdrawals due to adverse effects and are thus better tolerated as well as reducing systolic blood pressure more than calcium channel blockers.

Our review identified a likely decreased incidence of stroke events for diuretics compared with ACE inhibitors, and these findings are supported by other systematic reviews (Chen 2018; Psaty 2003). This advantage is in addition to diuretics being better tolerated and reducing systolic blood pressure to a greater extent.

The comparison of diuretics and alpha-blockers substantially favors thiazides and is supported by the network meta-analysis (Psaty 2003). For other classes of drugs we have one trial showing that diuretics are better tolerated than the centrally acting drug, clonidine. For angiotensin receptor blockers and renin inhibitors we lack head-to-head randomized controlled trial evidence, but there is no reason to expect that they would have any significant advantages.

We believe that the approach used in this review is the approach that should be used by groups developing hypertension guidelines. The fact that reduced clinically significant morbidity is achieved with first-line thiazides and thiazide-like drugs as compared to the other first-line drug classes should be reflected in all hypertension guidelines.

An important question arising from this review is why thiazides are better at reducing cardiovascular outcomes. It could be the fact that, as shown in this review, thiazides and thiazide-like diuretics reduce systolic blood pressure and thus pulse pressure to a greater degree than other drug classes. The common belief that different antihypertensive drug classes lower blood pressure by the same amount warrants a revisit, in view of the current substantial evidence from this review and others that indicate otherwise (Heran 2008a; Heran 2008b; Heran 2012a; Musini 2014).

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review have important implications for practice. These findings are relevant to the populations studied in these reviews, mostly older male and female hypertensive patients (aged 50 to 75) with multiple co-morbidities, including type 2 diabetes. This does represent the majority of the population treated for hypertension. As such, the results of this review are applicable to a wide spectrum of hypertensive patients, including those with type 2 diabetes. The findings are limited to first-line thiazide and thiazide-like diuretic drugs compared to beta-blockers, calcium channel blockers, ACE inhibitors, and alpha-blockers.

When first-line thiazides are compared to the other first-line antihypertensive drug classes, thiazides may reduce a number of clinically important morbidity outcomes. As compared to first-line beta-blockers, thiazides are likely not different in their effect on mortality, likely reduce total cardiovascular events, may have no effect on stroke, coronary heart disease (CHD), and heart failure, likely reduce withdrawals due to adverse effects, likely reduce systolic blood pressure, and likely have no effect on diastolic blood pressure.

As compared to first-line calcium channel blockers, first-line thiazides are likely not different in their effect on mortality, may have no effect on serious adverse events, likely reduce total cardiovascular events, likely have no effect on stroke or CHD, likely reduce heart failure, may reduce withdrawals due to adverse effects, likely reduce systolic blood pressure, and likely increase diastolic blood pressure.

As compared to first-line angiotensin converting enzyme (ACE) inhibitors, thiazides are likely not different in mortality, may not be different in total cardiovascular events, likely reduce stroke, likely have no effect on CHD or heart failure, likely reduce withdrawals due to adverse effects, likely reduce systolic blood pressure, and may reduce diastolic blood pressure.

As compared to first-line alpha-blockers, thiazides are likely not different in their effect on mortality, likely reduce total cardiovascular events and stroke, may have no effect on CHD, likely reduce heart failure, may reduce withdrawals due to adverse effects, likely reduce systolic blood pressure, and likely have no effect on diastolic blood pressure.

Data for comparison to other drug classes were insufficient, but no antihypertensive drug class had proven clinically important advantages over first-line thiazides.

Implications for research

It is important to note that there has been only one randomized trial designed and conducted to answer this question in the last 10 years (PREVER-treatment 2016). We hope that this review will encourage further trials. Future head-to-head trials assessing mortality and morbidity should include an arm with a first-line low-dose thiazide as the standard of therapy. Independent, large, long-duration head-to-head trials comparing first-line, low-dose thiazides with angiotensin receptor blockers and renin inhibitors are needed. Future research is needed to explore why thiazides are more effective at reducing some morbidity outcomes and better at lowering systolic blood pressure than other antihypertensive drug classes.

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- Sign-off Editor (final editorial decision): Michael Brown, Michigan State University College of Human Medicine, USA

- Managing Editor (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ALLHAT 2000/2002

Study characteristics	
Methods	Randomized, double-blind, active-controlled clinical trial
Participants	North American patients aged ≥ 55 with stage 1 or 2 hypertension and at least 1 other CHD risk factor 2000 analysis (chlorthalidone vs doxazosin): 24,335 patients; mean age, 67 years; 11,383 F:12,952 M 2002 analysis (chlorthalidone vs amlodipine vs lisinopril): 33,357 patients; mean age, 66.9 years; 15,638 F:17,719 M
Interventions	Chlorthalidone 12.5 mg to 25 mg daily Amlodipine 2.5 mg to 10 mg daily Lisinopril 10 mg to 40 mg daily Doxazosin 2 mg to 8 mg daily
Outcomes	Combined fatal CHD or non-fatal MI All-cause mortality Stroke (fatal and non-fatal) Combined CHD (the primary outcome, coronary revascularization, hospitalized angina) Combined CVD (combined CHD, stroke, other treated angina, HF (fatal, hospitalized, or treated non hospitalized), and peripheral arterial disease) BP at 1 year Duration: mean follow-up 3.2 years for doxazosin and 5 years for the other comparisons

ALLHAT 2000/2002 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ALLHAT 2002): "By telephone, participants were randomly assigned to chlorthalidone, amlodipine, or lisinopril in a ratio of 1.7:1:1. The concealed randomisation scheme was generated by computer, implemented at the clinical trials centre, stratified by centre and blocked in random block sizes of 5 or 9 to maintain balance." Quote (ALLHAT 2000): "... assigned by a computer-generated randomisation schedule to 1 of 4 treatments", 1:1:1:1. "Randomization was stratified by centre and blocked over time to maintain the ratio."
Allocation concealment (selection bias)	Low risk	Quote (ALLHAT 2000): "The randomisation code was held only by the ALLHAT Clinical Trials Center (CTC)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (ALLHAT 2002): "Step 1 drugs were encapsulated and identical in appearance so that the identity of each agent was double-masked at each dosage level." Supplemental therapy (step 2 and 3 drugs), as well as any other administered drugs (including low doses of open-label step 1 drug class), were administered open-label if patients failed to meet goal BP.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ALLHAT 2002): "Study outcomes were assessed at follow-up visits and reported to the clinical trials centre... In addition, searches for outcomes were accomplished through the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the National Death Index, and the Social Security Administration databases. A death was ascertained by clinic report or by match with the aforementioned databases plus a confirmatory death certificate... Medical reviewers from the clinical trials centre verified the physician-assigned diagnoses of outcomes using death certificates and hospital discharge summaries. More detailed information was collected on a random (10%) subset of CHD and stroke events to validate the procedure of using physician diagnoses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (ALLHAT 2002): "Data were analysed according to participants' randomised treatment assignments regardless of their subsequent medications (intent-to-treat analysis)." ALLHAT 2002 paper withdrawals at 5 years: figure 1. Total withdrawals: chlorthalidone 16%; amlodipine 15%; lisinopril 20%; WDAE chlorthalidone 2%; amlodipine 5%; lisinopril 3%; "Other nonmedical reasons" 1% each. Reasons and percentages seem comparable; no differential dropout. Cross-overs itemized and comparable. At trial closeout similar numbers had unknown vital status.
Selective reporting (reporting bias)	Low risk	All outcomes for this review were reported.
Use of supplemental drugs	High risk	Supplemental drugs and doses could be chosen from a predefined list at the discretion of study investigator, thus were not identical for all patients.

ALLHAT 2000/2002 *(Continued)*

		Quote (ALLHAT 2002): "For patients in any of the four treatment arms who are unable to attain satisfactory blood pressure control on the maximum tolerable dosage of their first-line drug, a choice of second- and third-line drugs are provided in open-label form for use in addition to (not substitution for) the first-line drug unless the first-line drug is not tolerated. The choice of second-line drug(s) is at the discretion of the treating study investigator". Step 2: atenolol 25 to 100 mg/day, reserpine 0.05 to 0.2 mg/day or clonidine 0.1 to 0.3 mg twice per day. Step 3: hydralazine, 25 to 100 mg twice per day.
Industry sponsorship	Low risk	Study was supported by contract with the National Heart, Lung, and Blood Institute (NHLBI). The ALLHAT investigators acknowledged contributions of study medications supplied by Pfizer Inc. (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin), and financial support provided by Pfizer to the NHLBI. The companies were not involved in the conduct, analysis or publication of the results of the trial.

ALPINE 2003

Study characteristics		
Methods	Double-blind, randomized, controlled, parallel-group trial	
Participants	392 patients from Sweden with hypertension (SBP 140 to 179 mmHg and/or DBP 90 to 104 mmHg), no severe concomitant disease including diabetes Mean age 55 years 207 F:185 M	
Interventions	Candesartan 16 mg daily Hydrochlorothiazide 25 mg daily	
Outcomes	BP at 1 year Patient well-being (subjective symptom assessment) Plasma glucose, serum insulin, OGTT Total plasma cholesterol, LDL-C, HDL-C, triglycerides AEs leading to withdrawal or change in therapy Duration: 12 months	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

ALPINE 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study indicates that participants were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as double-blind (including add-on treatment), but no additional details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat approach was used. Quote: "The discontinuation rates were low, 8.2 and 7.1% [for candesartan and hydrochlorothiazide], respectively." One patient was excluded from ITT due to lack of outcome data. PP analysis also reported. No patients were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Although there was no evidence of selective reporting and all outcomes in methods were reported, it is not possible to fully assess without a protocol that confirms the list of prespecified outcomes.
Use of supplemental drugs	High risk	Supplemental drugs differed between groups. Quote: "If sitting systolic or diastolic blood pressure was above the target pressure at any visit during the treatment period, double-blind treatment with 2.5–5.0 mg felodipine extended-release was added to the candesartan group and 50–100 mg atenolol was added to the hydrochlorothiazide group. No further antihypertensive treatment was allowed."
Industry sponsorship	High risk	Quote: "The study was financed by the Department of Public Health and Clinical Medicine, Umea University, Sweden together with AstraZeneca R&D, Mölndal, Sweden and Hassle Lakemedel AB, Sweden"

ANBP2 2003

Study characteristics	
Methods	Randomized, open-label trial
Participants	6083 patients in Australia aged 65 to 84 years with hypertension (SBP ≥ 160 mmHg or DBP ≥ 90 mmHg) Mean age 72 years 3102 F:2981 M
Interventions	Enalapril Hydrochlorothiazide

ANBP2 2003 *(Continued)*

	(recommended agents, although other ACE inhibitors and diuretics were permitted; doses not provided)
Outcomes	Combined endpoint of all cardiovascular events (coronary and cerebrovascular events, both fatal and nonfatal) or death from any cause Individually reported events: all-cause mortality, coronary event, MI, HF, cerebrovascular event, stroke BP at 1 year Duration: median follow-up 4 years
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study used an open-label design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An end-point committee whose members were unaware of the treatment group assignments adjudicated all potential end points."
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat analysis was used. Quote: "All subjects who underwent randomisation were included in the final analysis. For subjects who were lost to follow-up monitoring, we used the last available data; vital status was ascertained for all but two subjects." A total of 2.2% of patients in the ACE inhibitor group and 3.3% of patients in the diuretic group were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Without a protocol, cannot fully determine if all prespecified outcomes have been reported.
Use of supplemental drugs	High risk	Add-on therapy was permitted at physician's discretion with no clear algorithm. Since this was an open-label trial this could lead to bias. Quote: "To achieve the blood-pressure goals, the addition of beta-blockers, calcium-channel blockers, and alpha-blockers was recommended in both groups"
Industry sponsorship	High risk	Quote: "Supported by the Australian Commonwealth Department of Health and Aging; the National Health and Medical Research Council of Australia; and Merck Sharp & Dohme, Australia."

Berglund 1981

Study characteristics	
Methods	Randomized
Participants	106 male patients in Sweden with hypertension (SBP > 170 mmHg or DBP > 105 mmHg) Aged 47 to 54 (mean age not reported)
Interventions	Bendroflumethiazide 2.5 mg to 5 mg daily Propranolol 80 mg to 160 mg twice daily
Outcomes	OGTT, serum insulin Triglycerides, serum cholesterol Serum potassium, total body potassium, serum urate AEs Mortality BP at 1 year Duration: 12-month follow-up
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All 106 patients were maintained on the medication they were initially randomized to for the first year of follow-up. During the second to sixth year 4 patients in the bendroflumethiazide group (1 death) and 3 in the propranolol group (all deaths) were lost to follow-up." Analyzed those with 6 years of treatment (38 bendroflumethiazide and 37 propranolol) and according to original group regardless of treatment. About 30% no longer taking treatment of randomization. After 10 years of follow-up, 7 patients in the bendroflumethiazide group and 9 patients in the propranolol group died or were otherwise lost to follow-up.

Berglund 1981 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information about prespecified outcomes; unable to assess.
Use of supplemental drugs	Low risk	Dose increase was permitted but no supplemental drugs. Quote: "The dose was doubled to 5 mg bendroflumethiazide daily and 160 mg propranolol twice daily if after 2 months' treatment the BP was above 160 systolic or 95 mmHg diastolic. If the BP was not reduced below these limits by this dose increment, no further increment was made".
Industry sponsorship	Unclear risk	Quote: "This study was supported by a grant from the Swedish Association against Heart and Chest Diseases". Unclear if this organization receives sponsorship from for-profit companies.

DAPHNE 2002

Study characteristics	
Methods	Randomized, double-blind trial
Participants	80 male patients from the Netherlands, aged 45 to 70 years with essential hypertension (DPB 95 to 115 mmHg), peripheral atherosclerosis and hypercholesterolemia Mean age 59 years
Interventions	Doxazosin 1 mg to 16 mg daily Hydrochlorothiazide 12.5 mg to 100 mg daily
Outcomes	AEs Cholesterol, triglycerides, LDL-C, HDL-C, IDL-C Carotid intimal-medial thickness, femoral intimal-medial thickness BP at 1 year Duration: 3 years
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as double-blind, but no additional details provided.

DAPHNE 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was used. Quote: "A total of 29 patients [70.7%] in the doxazosin group and 27 [69.2%] in the HCTZ group completed the study." This represents a relatively large loss of patients with some difference between the 2 groups.
Selective reporting (reporting bias)	Unclear risk	Without a protocol, cannot fully determine if all prespecified outcomes have been reported.
Use of supplemental drugs	Low risk	Dose increase was permitted but no supplemental drugs. Quote: "Dose adjustment was allowed during the rest of the study when DBP was consistently above 90 mmHg. For doxazosin the regimen was 1 mg, 2 mg, 4 mg, 8 mg and 16 mg once a day; for HCTZ the dosing was 12.5 mg, 25 mg, 50 mg and 100 mg once a day."
Industry sponsorship	High risk	Quote: "The study was made possible by an unrestricted grant from Pfizer Netherlands BV."

HAPPHY 1987

Study characteristics	
Methods	Randomized, open-label trial
Participants	6569 male patients from 15 countries in Europe and North America aged 40 to 64 with hypertension (DBP 100 to 130 mmHg) Mean age 52 years
Interventions	Bendroflumethiazide 5 mg daily or hydrochlorothiazide 50 mg daily Atenolol 100 mg daily or metoprolol 200 mg daily
Outcomes	Serum potassium, creatinine, cholesterol, urate Mortality (cause-specific) Non-fatal MI Non-fatal stroke AEs BP at 1 year Duration: mean follow-up 3.8 years
Notes	—
Risk of bias	

Bias	Authors' judgement	Support for judgement

HAPPHY 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to open treatment with a diuretic or a beta-blocker, after stratification into nine groups according to predicted CHD risk based upon age, serum cholesterol, smoking habits and SBP... Individual centres could choose to use either atenolol or metoprolol and bendrofluazide or hyrochlorothiazide. The fact that there was no randomisation between centres choosing different alternatives, militated against a valid comparison of the two beta-blockers or of the two diuretics used in the trial." No further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were randomised to open treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent end-point committee reviewed the diagnoses of the end-points without knowing to which treatment patients had been randomised." Criteria for endpoints were well defined in the methods.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the crude withdrawal rate, calculated as the number of withdrawn patients divided by the total number of patients, was 8.9 and 7.9% in the diuretic and beta-blocker groups, respectively (NS), corresponding to an annual withdrawal rate of 2.4% per year for the diuretic treated group and 2.1 % for the beta-blocker treated group." Reasons for patient withdrawal are itemized and appear similar. Quote: "The analyses were made on an 'intention-to-treat' basis."
Selective reporting (reporting bias)	Unclear risk	Methods are well documented, but without a protocol, cannot fully determine if all prespecified outcomes have been reported.
Use of supplemental drugs	High risk	Additional treatment was consistent across first four steps, but was then free of choice in this non-blinded trial. Step 1: hydralazine (75 mg) Step 2: hydralazine (150 mg) Step 3: step 2 + spironolactone (75 mg) Step 4: step 2 + spironolactone (150 mg) Step 5: step 4 + optional drug Quote: "If the goal BP was not attained with the drugs and doses shown in the schedule, other drugs, free of choice, were added."
Industry sponsorship	High risk	Quote: "The trial was supported economically by AB Hassle, Mcilndal, a subsidiary of AB ASTRA, Sweden and ICI, Macclesfield, UK."

INSIGHT 2000

Study characteristics	
Methods	Randomized, double-blind trial

INSIGHT 2000 *(Continued)*

Participants	6321 patients from 8 countries (western Europe and Israel) aged 55 to 80 years with BP ≥ 150/95 mmHg or ≥ 160 mmHg SBP Mean age 65 years 3392 F:2929 M
Interventions	Nifedipine 30 mg daily Co-amilozide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily)
Outcomes	Composite endpoint of death from any cardiovascular or cerebrovascular cause, together with non-fatal stroke, MI, and HF Total mortality Death from vascular cause Non-fatal vascular events (including TIA, angina, renal failure) BP at 1 year AEs Duration: 1.75 years
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study used dynamic randomization (minimization). Quote: "As well as the risk factors in table 1, randomisation also took into account patients' sex, age, and whether or not they were receiving aspirin." No further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was double-blind. Quote: "All patients received one active and one placebo tablet taken at the same time of day." No further information provided on blinding of personnel and no details provided on the blinding or dose increases and add-on therapy for patients or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent critical events committee assessed all endpoints according to prespecified criteria. The members of this committee were unaware of the treatment group and blood pressure of each patient."
Incomplete outcome data (attrition bias) All outcomes	High risk	An intention-to-treat analysis was used. Total withdrawals were large and different between the 2 groups: 39.9% in the nifedipine group and 33.5% in the thiazide group. This high and different attrition in the 2 groups could lead to bias.

INSIGHT 2000 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Prespecified criteria no longer available on website; unable to assess.
Use of supplemental drugs	High risk	Additional treatment was consistent across first three steps, but was then based on clinician's choice. Quote: "There were four optional, dose-titration steps... These extra dose steps were: dose doubling of the randomised drug; addition of atenolol 25 mg daily (or enalapril 5 mg daily if atenolol contraindicated); dose-doubling of the additional drug; and addition of any other antihypertensive drug (other than calcium-channel blockers or diuretics). These titration steps could be done in that order at any visit".
Industry sponsorship	High risk	Quote: "The study was funded conducted and reported by Bayer AG".

Materson 1993

Study characteristics		
Methods	Randomized, double-blind, placebo-controlled study for a period of 1 year	
Participants	1292 male veterans with resting diastolic blood pressure of 95 mmHg to 109 mmHg	
Interventions	Placebo or 1 of the 6 drugs: hydrochlorothiazide 12.5 mg to 50 mg/day; atenolol 25 mg to 100 mg/day; captopril 25 mg to 100 mg/day; clonidine 0.2 mg to 0.6 mg/day; a sustained preparation of diltiazem 120 mg to 360 mg/day or prazosin 4 mg to 20 mg/day	
Outcomes	Withdrawals due to adverse effects Duration 1 year	
Notes	Morbidity and mortality not reported. Blood pressure not reported at 1 year.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not reported.
Allocation concealment (selection bias)	Unclear risk	Method of achieving allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding maintained.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of withdrawals due to adverse effects outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of withdrawals in each arm.

Materson 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	Withdrawals due to adverse effects reported in each group.
Use of supplemental drugs	Low risk	No supplemental drugs allowed.
Industry sponsorship	Low risk	Veterans administration trial. No industry involvement.

MIDAS 1996

Study characteristics	
Methods	Multicenter, randomized, double-bind, controlled clinical trial
Participants	883 patients in the USA aged ≥ 40 years with DBP 90 to 115 mmHg Mean age 58 years 194 F:689 M
Interventions	Hydrochlorothiazide 12.5 mg to 25 mg twice daily Isradipine 2.5 mg to 5.0 mg twice daily
Outcomes	IMT Any major vascular event (stroke, MI, CHF, angina, sudden death and other cardiovascular disease-related death) Any major vascular procedure (endarterectomy, CABG and angioplasty) Any non-major vascular events/procedures (TIA, AF, PVC, femoral/popliteal bypass graft, aortic valve replacement and palpitation) BP at 1 year Duration: 3 years
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients... were randomised into 2 treatment groups... The randomisation process was stratified and blocked by clinic to provide equal probability of assignment to either treatment group throughout the study."
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided, although add-on enalapril, if used, was administered open-label.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as double-blind, but no additional details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All reported clinical events were reviewed, adjudicated, and classified by the MIDAS Investigators' Morbidity and Mortality Committee, consisting of 6 clinicians, each from a different clinical centre; all were blinded to the

MIDAS 1996 *(Continued)*

		randomisation assignments... Members of this committee were required to reach a unanimous decision, based on clinical judgment, on how each reported event should be classified." Quote: "After completion of the trial, when investigators were unblinded to the results on clinical events obtained by the Morbidity and Mortality Committee, concern was expressed as to whether objective criteria had been consistently applied in adjudication of clinical events, especially those classified as 'hospitalized angina pectoris'. Accordingly an external ad hoc panel of 3 recognized authorities in the fields of cardiology and epidemiology was appointed. Using standard clinical definitions and the hierarchy described herein, this ad hoc committee independently reviewed and adjudicated selected clinical events while blinded to the randomisation assignments of the participants. The final analysis of clinical events reported in this article is based on the classification of events reported by this ad hoc committee." Because unblinding occurred (and was the reason for the ad hoc committee), risk is assessed as unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat approach was used. Quote: "[At the study end] Twenty percent of those on isradipine treatment and 18% of those on hydrochlorothiazide treatment had withdrawn from their respective study medications." Relatively high attrition over 3 years.
Selective reporting (reporting bias)	Low risk	All cardiovascular and BP outcomes in the protocol reported.
Use of supplemental drugs	Low risk	Only enalapril permitted for add-on therapy. Quote: "Those who do not have responses (whose diastolic blood pressure is not controlled) to the first dose of the study drugs will have their doses doubled. The small proportion of participants who then still do not demonstrate adequate blood pressure control will receive open-label enalapril in doses from 2.5 to 10 mg twice daily."
Industry sponsorship	High risk	Quote: "This study was supported in part by Sandoz Research Institute (SRI), Sandoz Pharmaceuticals, East Hanover, NJ".

MRC 1985

Study characteristics	
Methods	Randomized controlled trial
Participants	17,354 patients in the UK aged 35 to 64 with hypertension (DBP 90 to 109 mmHg; SBP < 200 mmHg) Mean age 52 years 8306 F:9048 M
Interventions	Bendrofluazide 10 mg daily Propranolol up to 240 mg daily Placebo
Outcomes	Stroke Coronary events

MRC 1985 *(Continued)*

	All CV events All-cause mortality BP at 1 year Duration: 5.5 years
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated at entry... Randomisation was in stratified blocks of eight within each sex, 10 year age group, and clinic." No information provided for sequence generation.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "four treatments: the thiazide diuretic bendrofluazide; placebo tablets that looked like bendrofluazide; the beta blocker propranolol; and placebo tablets that looked like propranolol. The two placebo groups were treated as one in all analyses." Quote: "When the protocol was written, it was judged unreasonable to ask general practitioners to undertake such adjustments in a double blind study, and the trial was therefore single blind only."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evidence on which the diagnosis of each terminating event was based was assessed by an arbitrator ignorant of the treatment regimen... The arbitrator used WHO criteria for classification." Adjudication was independent and blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "All analyses presented here are based on randomised treatment ("intention to treat") categories. Thus data for all participants are presented as if the individual was still in the treatment group to which he was originally randomised, although substantial percentages of patients (see below) were in fact withdrawn from their randomly allocated regimen during follow up." Quote: "The total five and a half year cumulative percentages of men who stopped taking their randomised treatment, including both those withdrawn from their randomly allocated regimen but continuing on follow up and those lapsing from the trial, were 43% of the bendrofluazide group, 42% of the propranolol group, and 47% of the placebo group. For women the figures were 33%, 40%, and 40% respectively. The cumulative percentages of people not taking either primary active drug by five and a half years were smaller: 33% of men originally randomised to bendrofluazide and 34% of men randomised to propranolol and 28% and 31% respectively of women."
Selective reporting (reporting bias)	Unclear risk	No information about prespecified outcomes is available on which to make this assessment.
Use of supplemental drugs	High risk	Supplemental drugs differed between groups for a portion of the study. Quote: "Supplementary treatment was added if blood pressure did not respond satisfactorily to the primary drug. Methyldopa was originally used as a supplement

MRC 1985 *(Continued)*

		to bendrofluazide and guanethidine as a supplement to propranolol, but later methyldopa was used whatever the primary drug." The primary paper does not report proportion who were initially treated with different supplementary drugs.
Industry sponsorship	High risk	Quote: "The working party thanks... Flockhart and Co Ltd for tablets of bendrofluazide and placebo; Imperial Chemical Industries Ltd for financial support and for tablets of propranolol and placebo; CIBA Laboratories for supplies of guanethidine; and Merck Sharp and Dohme Ltd for a mobile screening unit, funds for its staffing, and supplies of methyldopa."

MRC 1992

Study characteristics	
Methods	Randomized, placebo-controlled, single-blind trial
Participants	4396 patients in the UK aged 65 to 74 with hypertension (SBP 160 to 209 mmHg; DBP < 115 mmHg) Mean age 70 years 2560 F:1836 M
Interventions	Amiloride 2.5 to 5 mg daily and hydrochlorothiazide 25 to 50 mg daily Atenolol 50 mg Placebo
Outcomes	Stroke (fatal or non-fatal) Coronary events (sudden death due to coronary cause, fatal and non-fatal MI) Other cardiovascular events All-cause mortality BP at 1 year Duration: mean follow-up 5.8 years
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "All trial entrants were randomly allocated in equal proportions to one of four treatment categories... Randomisation was in stratified blocks of eight within each sex and clinic." No information provided for sequence generation.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.

MRC 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The trial was single blind: patients did not know which treatment group they were in, but the doctors and nurses did."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The diagnostic evidence for each terminating event was assessed by an arbitrator, blind to the treatment regimen. World Health Organisation criteria for classification of strokes and coronary events were used. All available documentation was reviewed, including copies of general practitioners' notes, hospital inpatient or outpatient notes..."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The primary results are based on a comparison of groups according to their randomised treatment - that is, on an intention to treat basis." Quote: "Over the five and a half years about 25% of people were lost to follow up. The cumulative percentages of people who stopped taking their randomised treatment, including both those withdrawn but continuing on follow up and those lost to follow up, were 48% of the diuretic group, 63% of the beta-blocker group, and 53% of the placebo group." Insufficient detail to determine if ITT was carried out correctly. Differential dropouts in terms of reasons (beta-blocker group had more withdrawals, for both suspected major side effects (333 WDAE, 12 inadequate control); diuretic 160 WDAE and 1 inadequate control; placebo 82 WDAE and 175 inadequate control).
Selective reporting (reporting bias)	Unclear risk	Outcomes not identified as prespecified (other than the outcome on which a sample size calculation was reported); unable to assess.
Use of supplemental drugs	High risk	Quote: "Drug regimens for those on active treatment were modified if blood pressure had not responded after 12 weeks or if target pressure had not been achieved after six months. The most common change necessary was an increase in atenolol to 100 mg daily (225 patients). When further control was necessary the other trial drug was used to supplement the drug allocated by randomisation. After this, the calcium channel blocker nifedipine was used in doses of up to 20 mg daily. Any other supplementary drugs were also allowed at this stage (further details on request)." There is potential confounding by the fact that the other drug was used in treatment arms; 11% to 16% of patients received the drug opposite to the one they were assigned.
Industry sponsorship	Low risk	MRC funded trial. Only the drugs were supplied by the different companies.

NESTOR 2004

Study characteristics	
Methods	Randomized, multinational, double-blind, double-dummy, parallel-group trial
Participants	570 patients from 18 countries with type 2 diabetes, essential hypertension (SBP 140 to 180 mmHg, DBP < 110 mmHg) and persistent microalbuminuria (20 to 200 g/min) Mean age 60 years 71 F:129 M

NESTOR 2004 *(Continued)*

Interventions	Indapamide SR 1.5 mg daily Enalapril 10 mg daily
Outcomes	AEs UACR, AER, creatinine clearance, fractional albumin clearance BP at 1 year Duration: 1 year
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients who fulfil all of the inclusion criteria will be randomly allocated- to one of the two study treatments by a computerized randomisation procedure."
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was double-blind and double-dummy. Quote: "Treatment will be administered daily in the form of one tablet (indapamide SR or placebo) plus one capsule (enalapril or placebo)." Supplemental drugs were administered in an open-label fashion.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All ABPM recordings were edited by the investigators and sent to the Central Committee for validation by an expert.... Assessment of safety was based mainly on analysis of adverse events, ECG parameters, body mass index and biochemical parameters." Unclear if assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat analysis was used. Quote: "Two hundred and forty-seven (87%) and 255 (89%) patients completed the study at week 52 in the indapamide SR and in the enalapril groups, respectively."
Selective reporting (reporting bias)	Low risk	All cardiovascular and blood pressure outcomes listed in the protocol were reported.
Use of supplemental drugs	Low risk	Stepped treatment algorithm was the same for all participants. Quote: "From week 6 of the double-blind period, the addition of open label treatment will be possible, with amlodipine 5 to 10 mg once daily as a first step and atenolol 50 to 100 mg once daily as a second step."
Industry sponsorship	High risk	Quote: "This study was supported by an unrestricted grant from Institut de Recherches Internationales Servier"

NICS-EH 1999

Study characteristics	
Methods	Phase IV, multicenter, randomized, double-blind, controlled, comparative clinical trial
Participants	414 patients in Japan aged 60 and older with hypertension (SBP 160 to 220 mmHg and DBP < 115 mmHg) with no history of cardiovascular complications Mean age 70 years 277 F:137 M
Interventions	Trichlormethiazide 2 mg daily Nicardipine 20 mg twice daily
Outcomes	Cardiovascular complications Erythrocyte count, total leucocyte count, hemoglobin concentration, hematocrit, total protein, albumin, total bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, lactate dehydrogenase, sodium, potassium, chlorine, calcium, phosphorus, blood urea nitrogen, creatinine, uric acid, blood glucose, triglycerides, total cholesterol, high-density lipoprotein-cholesterol, urinary protein, urinary glucose and urinary sediments AEs BP at 1 year Duration: 5 years
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy method was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "For patients who had any end point, the attending physician's judgment was assessed blindly by the Steering Committee and the diagnosis was confirmed."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Per protocol analysis was used to analyze the results of this trial" At week 140, 101 patients (50.2%) remained in the trichlormethiazide group and 84 patients (41.2%) remained in the nicardipine group. High and differential dropouts.
Selective reporting (reporting bias)	Low risk	Protocol published with interim analyses; does not appear to be evidence of selective outcome reporting.
Use of supplemental drugs	Low risk	Dose increase was permitted but no supplemental drugs.

NICS-EH 1999 *(Continued)*

		Quote: "The dosage was increased by up to 2-fold when the antihypertensive effect achieved was not sufficient. The only antihypertensive agents allowed were the trial drugs, although a potassium supplement was administered when necessary".
Industry sponsorship	Unclear risk	No specific indication of any funding or sponsorship.

PHYLLIS 2004

Study characteristics	
Methods	Randomized, double-blind trial
Participants	508 patients from Italy with hypertension (SBP 150 to 210 mmHg, DBP 95 to 115 mmHg), hypercholesterolemia and asymptomatic carotid atherosclerosis Mean age 58 years 304 F:204 M
Interventions	Hydrochlorothiazide 25 mg daily plus placebo Fosinopril 20 mg daily plus placebo Hydrochlorothiazide 25 mg daily plus pravastatin 40 mg daily Fosinopril 20 mg daily plus pravastatin 40 mg daily
Outcomes	IMT Total cholesterol, LDL-C, HDL-C, triglycerides Glucose, creatinine, urate, potassium MI, stroke and CVD events BP at 1 year Duration: 2.6 years
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was computer generated with a block size of 4."
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients and study personnel were blinded to treatment assignment." Placebos were used to maintain blinding (triple-dummy system). Add-on therapy was permitted in an open-label fashion.

PHYLLIS 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An intention-to-treat analysis was used. No information on patient discontinuations was provided.
Selective reporting (reporting bias)	Unclear risk	No information about prespecified outcomes is available on which to make this assessment.
Use of supplemental drugs	Low risk	Only nifedipine was permitted as add-on therapy. Quote: "If DBP was not >90 mm Hg or >95 mm Hg with a fall of ≥10 mm Hg, open-label nifedipine gastrointestinal therapeutic system (GITS), 30 mg QD, was added after 3 months to be eventually increased to 60 mg after 6 months."
Industry sponsorship	High risk	Quote: "PHYLLIS was an investigator-generated trial sponsored by Bristol-Myers Squibb Italy, Rome, and Menarini, Florence. All authors have received research grants or lecture honoraria from the sponsors."

PREVER-treatment 2016

Study characteristics	
Methods	Randomized, double-blind trial
Participants	655 patients aged 30 to 70 years from Brazil with hypertension (SBP 140 to 159 mmHg or DBP 90 to 99 mmHg) after a 3-month lifestyle intervention phase Mean age 54 years 321 F:334 M
Interventions	Chlorthalidone/amiloride 12.5 mg to 25 mg/2.5 mg to 5 mg daily Losartan 50 mg to 100 mg daily Optional add-on: amlodipine 5 mg to 10 mg daily (month 6 and 9) followed by propranolol 40 mg to 80 mg twice a day (month 12 and 15)
Outcomes	Proportion of patients with controlled hypertension Use of non-study BP-lowering medications Development or worsening of microalbuminuria and left ventricular mass Fatal and nonfatal major cardiovascular events Safety BP at 1 year Duration: 18 months
Notes	—
Risk of bias	

PREVER-treatment 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... participants were randomly assigned in a 1:1 ratio to a chlorthalidone along with amiloride combination pill or to losartan. Randomization was based on a computer-generated list, using validated software, with variable block sizes of 4, 6, 8, or 10 and was stratified by center."
Allocation concealment (selection bias)	Low risk	Quote: "To guarantee concealment of the allocation list, randomization was implemented through a 24-h web-based automated system."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Participants, members of the steering committee, healthcare staff... were blinded as to whether patients received chlorthalidone/amiloride or losartan...The two study drugs were identical in size, shape, color, taste, and texture." However, the add-on drugs amlodipine and propanolol were open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "... outcome assessors but not members from the data safety monitoring committee were blinded as to whether patients received chlorthalidone/amiloride or losartan."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Methods state that "Trial results were analyzed using the intention-to-treat approach"; however, patients with incomplete follow-up do not appear to have been included in the evaluation of outcomes. Dropouts: chlorthalidone/amlodipine: 6.9%; losartan: 7.1%; reasons for withdrawals generally similar. Evaluation at 18 months: chlorthalidone/amlodipine 310/333 (93.1%); losartan 299/322 (92.9%). Follow-up included 27 participants off trial drugs in diuretic arm and 31 in other arm. Handling of dropouts: analysis stated as "intention-to-treat". Use of a random-effects linear model with adjustment for within-participant correlation among the longitudinal data; model included an indicator variable for time, an interaction term for treatment by time, and the variable treatment. Quote: "Results or imputed estimates were included from participants who were lost to follow-up, who had minor protocol deviations, such as missing one or more visits or measurement of only one BP value at a study visit, and whose study visits occurred on days other than scheduled."
Selective reporting (reporting bias)	Low risk	Published protocol identified the following outcomes: BP variation; proportion of use of add-on drugs; adverse events; development of worsening of microalbuminuria; left ventricular hypertrophy (ECG); fatal or major cardiovascular events. All were reported. Ambiguous information was clarified with authors.
Use of supplemental drugs	Low risk	Stepped treatment algorithm was the same for all patients. Quote: "At the third month study visit, the dose was doubled if BP remained uncontrolled. If BP was uncontrolled at the 6-month visit, amlodipine 5mg once a day was added, in an open fashion, and increased to 10mg if necessary at the 9-month visit. At the 12-month visit, propranolol 40 twice a day was prescribed for patients with uncontrolled BP, and doubled at the fifteenth month visit if necessary."
Industry sponsorship	Low risk	Quote: "Sources of funding: this study was funded by grants from the Department of Science and Technology (DECIT), Health Ministry; National Council of Research (CNPq) and Agency for Funding of Studies and Projects (FINEP),

PREVER-treatment 2016 *(Continued)*

	Science and Technology Ministry; National Institute of Health Technology Assessment (IATS); and Funding of Incentive to Research (FIPE), Hospital de Clinicas de Porto Alegre, all in Brazil. The sponsors had no participation in the design and conduct of the study, preparation and approval of the manuscript."

Schmieder 2009

Study characteristics	
Methods	Randomized, double-blind, active-controlled, dose-titration trial followed by an extension phase
Participants	1124 patients from 6 European countries with hypertension (SBP 140 to 179 mmHg and/or DBP 90 to 104 mmHg), no severe concomitant disease and no diabetes Mean age 56 years 505 F:618 M
Interventions	Aliskiren 150 mg to 300 mg daily Hydrochlorothiazide 12.5 mg to 25 mg daily Optional add-on treatment of amlodipine 5 mg to 10 mg daily
Outcomes	AEs Potassium, creatinine, BUN BP at 1 year Duration: 1 year
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization by centre was performed by the interactive voice response system provider with the use of a validated system that automates the random assignment of patients to randomisation numbers." Unclear if patients who were initially randomized to placebo treatment were then assigned to aliskiren or hydrochlorothiazide at 6 weeks in a randomized manner.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization data were kept strictly confidential until the time of unblinding."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as double-blind, but no additional details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.

Schmieder 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An intention-to-treat analysis was used. Quote: "[During the 26-week double-blind period] the overall number of discontinuations was significantly higher with the hydrochlorothiazide regimen than with the aliskiren regimen (15.8% versus 10.2%, respectively)." Quote: "[During the 26-week extension] the proportion of patients discontinuing in this phase of the study was higher with the hydrochlorothiazide regimen than with the aliskiren regimen (6.7% versus 3.2%, respectively)."
Selective reporting (reporting bias)	Unclear risk	Unable to fully assess (no available protocol listing prespecified outcomes).
Use of supplemental drugs	Low risk	Only amlodipine permitted as add-on therapy. Quote: "For patients not achieving the target BP of less than 140/90 mmHg, addition of amlodipine 5 mg was permitted from week 12, with titration to 10 mg from week 18."
Industry sponsorship	High risk	Quote: "This study was supported by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA."

SHELL 2003

Study characteristics	
Methods	Randomized, double-blind trial
Participants	1882 patients from Italy aged ≥ 60 with SBP ≥ 160 mmHg and DBP ≤ 95 mmHg Mean age 72 years 1154 F:728 M
Interventions	Chlorthalidone 12.5 mg to 25 mg daily Lacidipine 4 mg to 6 mg daily
Outcomes	Composite of fatal and non-fatal stroke, sudden death, fatal and non-fatal myocardial infarction, fatal and nonfatal congestive heart failure, myocardial revascularization and carotid endarterectomy All-cause mortality TIA Non-Q myocardial infarction AEs BP at 1 year Duration: up to 5 years
Notes	—
Risk of bias	

SHELL 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was made by BETA Trial Center, Genoa (Italy), using a sequentially based criterion."
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was conducted in an open fashion. However, in 12 additional centers, patients were followed in double-blind fashion for the first year of treatment to evaluate objectively the efficacy and tolerability of the drugs employed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Events were assessed according to predefined criteria by an independent committee unaware of the treatment group to which patients belonged."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During follow-up, patients who remained on randomised treatment were 79.5% in the lacidipine group and 75.5% in the chlorthalidone group." Quote: "Data were analysed on an intention-to-treat basis by BETA Trial Center."
Selective reporting (reporting bias)	High risk	All primary outcomes are listed in results; "non-Q myocardial infarction" was listed as a secondary outcome but it is not mentioned in the results. Protocol listing prespecified outcomes not available.
Use of supplemental drugs	Low risk	Any ACE inhibitor permitted. Quote: "If the systolic blood pressure response was not satisfactory (reduction ≤20 mmHg and absolute value >160 mmHg) at the end of the first 4 weeks, treatment was titrated upward first by increasing the dose of the initial monotherapy (chlorthalidone 25 mg and lacidipine 6 mg) and by bringing back the monotherapy dose to the initial step and adding fosinopril 10 mg o.d. or any other ACE inhibitor at an equivalent dose after another 4 weeks of treatment."
Industry sponsorship	High risk	Quote: "The trial was sponsored by Laboratori Guidotti s.p.a., Pisa, Italy."

Tresukosol 2005

Study characteristics	
Methods	Randomized
Participants	200 patients aged 60 to 80 years with well-established history of mild to moderate isolated systolic hypertension (SBP > 160 mmHg, DBP < 90 mmHg) Mean age 69 years 68 F:32 M
Interventions	Amlodipine 5 mg to 10 mg daily Hydrochlorothiazide 25 mg to 50 mg daily
Outcomes	LVMI

Tresukosol 2005 *(Continued)*

	Death MI, stroke AEs Cost of treatment BP at 1 year Duration: 1.5 years
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study indicates that participants were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analysis; no indication of an intention-to-treat analysis. A total of 27.5% of participants discontinued treatment from the amlodipine group, whereas 12.2% of participants discontinued from the hydrochlorothiazide group (differential dropout rate).
Selective reporting (reporting bias)	Unclear risk	Unable to fully assess (no available protocol listing prespecified outcomes)
Use of supplemental drugs	Low risk	Only prazosin permitted as add-on therapy. Quote: "After the 6-month ECHO measurement, only Prazosin 1-20 mg per day could be added for those who had sitting systolic blood pressure above 160 mmHg in order to achieve optimal sitting systolic blood pressure below 140 mmHg."
Industry sponsorship	Low risk	Supported by grants of the National Research Council of Thailand.

VA 1982

Study characteristics

Methods	Multicenter, randomized, double-blind trial

VA 1982 *(Continued)*

Participants	683 male patients aged 21 to 65 years with hypertension (DBP 95 to 114 mmHg) Mean age 50 years
Interventions	Propranolol 80 mg to 640 mg daily Hydrochlorothiazide 50 mg to 200 mg daily
Outcomes	Reasons for discontinuation AEs Blood chemistry BP at 1 year Duration: 12 months
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blind. Quote: "The code name for the identical appearing tablets containing either propranolol or hydrochlorothiazide was 'propazide.' The six strengths of both preparations were referred to as propazide B, C, D, E, F, and G."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of outcome assessment blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Among the 394 patients who entered the long-term treatment phase, 302 completed the 12 month follow-up, while 92 were terminated... Administrative reasons for termination included 14 patients receiving propranolol and 18 receiving hydrochlorothiazide... More terminations owing to medical causes occurred in the propranolol group as compared with the patients receiving hydrochlorothiazide. There were 46 medical terminations, of which 35 were associated with propranolol and 11 with hydrochlorothiazide (P<.001)," Unclear how missing data were accounted for in patients who dropped out. Differential dropout in terms of reason for withdrawal.
Selective reporting (reporting bias)	Unclear risk	Unable to fully assess (no available protocol listing prespecified outcomes).
Use of supplemental drugs	Low risk	Dose increase was permitted but no supplemental drugs.
Industry sponsorship	High risk	Quote: "This study was supported by a grant from Ayerst Laboratories, Inc."

VHAS 1997

Study characteristics	
Methods	Multicenter, randomized, parallel-group trial
Participants	1414 patients in Italy aged 40 to 65 years with hypertension (msSBP ≥ 160 and msDBP ≥ 95 mmHg) Mean age 54 years 722 F:690 M
Interventions	Chlorthalidone 25 mg daily Verapamil 240 mg daily
Outcomes	ECG Serum glucose, creatinine total and HDL-C, triglycerides, urate, BUN, AST, ALT, sodium and potassium AEs Cardiovascular events (stroke, MI, TIA, angina, HF, revascularization procedures) BP at 1 year Duration: 2 years
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study indicates that patients were randomly allocated to treatment groups, but no further information provided regarding the method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "After the first 6 months of double-blind treatment, the patients returned to being administered their previous treatment according to an open design for an additional 18 months (open treatment)." No details provided on measures used to achieve double-blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The details of cardiovascular events were verified, according to predetermined criteria, by experts blind to the randomised treatment assigned". Unclear if physicians conducting the clinical examinations throughout the study were blind to treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "1464 entered the run-in period and 1414 were allocated randomly to double-blind treatment. All of them made at least one visit during the treatment period and could be included in intention-to-treat analyses... In total 1099 patients completed the 2-year treatment period; 315 dropped out (21.6% of the verapamil group and 22.9% of the chlorthalidone group)." Unclear how missing data were accounted for in participants who dropped out. Per-protocol analysis also reported.

VHAS 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	Assessment is based on predetermined criteria for cardiovascular events.
Use of supplemental drugs	Low risk	Only captopril permitted as add-on treatment. Quote: "After 1 month, we added 25 mg captopril once a day to the double-blind treatment for patients whose blood pressures had not been lowered to the goal values (a DBP while sitting < 90 mmHg or < 95 mmHg with a reduction of at least 10% from baseline values). After the second month we increased the captopril dose to 25 mg twice a day for patients whose blood pressures had not yet responded to the combined treatment."
Industry sponsorship	High risk	No specific indication of any funding or sponsorship in primary manuscript but in 1998 paper substudy in the *Journal of Hypertension* (16(11):1667-76) quote: "This study was supported by a scientific grant from Knoll Farmaceutici Spa and Ravizza Farmaceutici Spa".

ABPM: ambulatory blood pressure monitoring; **ACE:** angiotensin converting enzyme; **AER:** albumin excretion rate; **AEs:** adverse events; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **BP:** blood pressure; **BUN:** blood urea nitrogen**; CABG:** coronary artery bypass graft; **CHD:** coronary heart disease**; CHF:** chronic heart failure; **CVD:** cardiovascular disease; **DBP:** diastolic blood pressure; **ECG:** electrocardiogram; **F:** female; **HDL:** high-density lipoprotein; **HF:** heart failure; **IMT:** intimal-medial thickness; **ITT:** intention-to-treat; **LDL:** low-density lipoprotein; **LVMI:** left ventricular mass index; **M:** male; **MI:** myocardial infarction; MRC: medical research council; **ms:** mean sitting; **OGTT:** oral glucose tolerance test; **PP:** per protocol; **PVC:** premature ventricular complex; **SBP:** systolic blood pressure; **TIA:** transient ischemic attack; **UACR:** urine albumin-creatinine ratio; **WDAE:** withdrawal due to adverse event

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACCOMPLISH 2008	Control group was combination therapy not a single first-line drug class
Appel 2010	No diuretic monotherapy treatment group
AVEC 2012	No primary outcomes reported
Bakris 2010	No diuretic monotherapy treatment group
Bebb 2007	No diuretic monotherapy treatment group
Caruso 2004	No primary outcomes reported
Cho 2008	Treatment duration < 12 months
COLM investigators 2014	Combination therapy and not first-line single drug class
CONVINCE 2003	Data for patients treated with diuretic monotherapy pooled with other treatment groups; no diuretic monotherapy data available from publication
Cooper-DeHoff 2010	Treatment duration < 12 months
COPE 2011	Assesses diuretics in combination with calcium channel blockers after initial failure of calcium channel blockers alone
COSMO-CKD 2014	No diuretic monotherapy; patients on background RAS inhibitor
Ebbs 2001	Treatment duration < 12 months

Study	Reason for exclusion
Galzerano 2004	No primary outcomes reported
GENRES 2007	Treatment duration < 12 months
Grassi 2006	No primary outcomes reported; BP data only
Iyalomhe 2014	Treatment duration < 12 months
Jordan 2012	Treatment duration < 12 months
Khan 2008	Treatment duration < 12 months
Klingbeil 2000	Treatment duration < 12 months
LIFE 2002	No diuretic monotherapy treatment group
LIVE 1998	Treatment duration < 12 months; median follow-up of 11 months
Mahmud 2009	Congress abstract only; no primary outcomes reported and duration of treatment unclear
Mallion 2004	No active comparator assessed
Mann 2002	Treatment duration < 12 months
Morgan 2004	Treatment duration < 12 months
Neaton 1993	Outcomes were not reported separately for different comparators; study authors were contacted but refused to provide data separately for different groups
NORDIL 2000	Data for patients treated with diuretic monotherapy pooled with other treatment groups; no diuretic monotherapy data available from publication
Oshchepkova 2007	Treatment duration < 12 months
PEAR 2012	Treatment duration < 12 months
Peng 2015	Inappropriate patient group (high-normal at baseline; not hypertensive)
Pool 2009	Treatment duration < 12 months
Posadzy-Malaczynska 2014	No primary outcomes reported
PROGRESS 2001	No diuretic monotherapy treatment group
Rasmussen 2006	Treatment duration < 12 months
SALT 2007	Treatment duration < 12 months
Schram 2005	No primary outcomes reported; BP data only
Schwartz 2013	Treatment duration < 12 months
SHEP 1991	Systolic Hypertension in the Elderly Program (SHEP) trial; no head-to-head comparison with another active comparator

Study	Reason for exclusion
Shionoiri 2000	No primary outcomes reported; BP data only
Sierra 2004	Congress abstract only; no primary outcomes reported.
Solorzano 2011	Congress abstract; retrospective analysis of trial data but unclear if RCT
SPREAD 2006	Outcomes not relevant; BP data only
STOP-Hypertension-2 1999	Data for patients treated with diuretic monotherapy pooled with other treatment groups; no diuretic monotherapy data available from publication
Stritzke 2010	Congress abstract only; no primary outcomes reported
Syst-Eur 1997	No diuretic monotherapy treatment group
Tedesco 1998	No primary outcomes reported
Tedesco 1999	No primary outcomes reported
Trimarco 2011	Congress abstract only; insufficient data regarding primary outcomes
Trimarco 2015	No primary outcome data reported; abstract only
VADT 2011	No diuretic monotherapy treatment group
Veronesi 2007	No primary outcomes reported
Wilson 1963	No primary outcomes reported
Yasuda 2015	Treatment duration < 12 months
Yogiantoro 2000	Congress abstract only; no primary outcomes reported
Yurenev 1992	Patients with left ventricular hypertrophy were included, not specifically a hypertension population. Study was included in Thomopoulos 2015 systematic review.

BP: blood pressure; **RAS:** renin angiotensin inhibitors; **RCT:** randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02217852

Study name	NCT02217852
Methods	Randomized, open-label, controlled clinical trial
Participants	Adult Tibetan patients with diagnosed hypertension grade 1 to 3, aged 18 to 80 years old
Interventions	Nitrendipine 10 to 20 mg orally twice daily Hydrochlorothiazide 12.5 mg to 25 mg orally 4 times daily Captopril plus hydrochlorothiazide, 25 mg to 50 mg orally 3 times for captopril and 12.5 to 25 mg orally 4 times a day for hydrochlorothiazide

NCT02217852 *(Continued)*	Beijing hypotensive No.0, 1 pile orally 4 times a day or less
Outcomes	Change in blood pressure (12 months), change in target organ damage
Starting date	August 2014
Contact information	Xiaoping Chen, MD, West China Hospital, Chengdu, Sichuan, China, 610041 xiaopingchen11@126.com
Notes	—

DATA AND ANALYSES

Comparison 1. First-line diuretics versus active comparators: primary outcomes

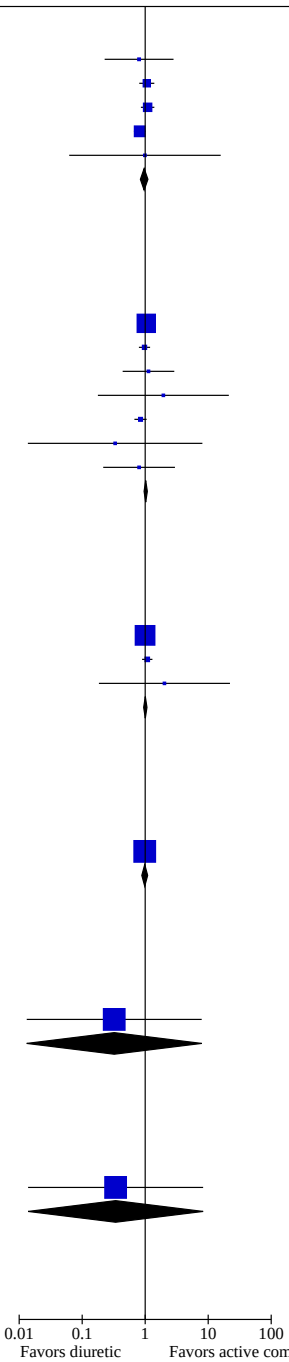
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total mortality	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 vs beta-blockers	5	18241	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]
1.1.2 vs calcium channel blockers	7	35417	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.08]
1.1.3 vs ACE inhibitors	3	30961	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.07]
1.1.4 vs alpha adrenergic blockers	1	24316	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.09]
1.1.5 vs angiotensin II receptor blockers	1	655	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.88]
1.1.6 vs direct renin inhibitors	1	1124	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.31]
1.2 Total serious adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 vs calcium channel blockers	2	7204	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.97, 1.24]
1.2.2 vs direct renin inhibitors	1	1124	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.50]
1.3 Total cardiovascular events	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 vs beta-blockers	4	18135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 1.00]
1.3.2 vs calcium channel blockers	6	35217	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.89, 0.98]
1.3.3 vs ACE inhibitors	3	30900	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.02]

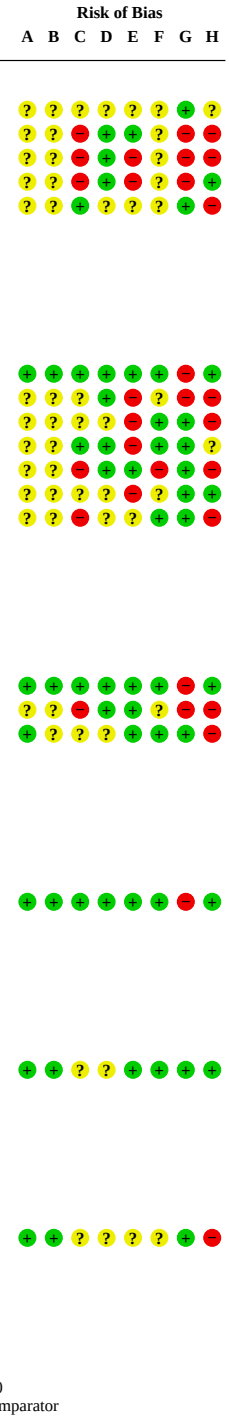
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.4 vs alpha adrenergic blockers	2	24396	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.69, 0.80]
1.3.5 vs angiotensin II receptor blockers	2	1047	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.25, 8.79]
1.4 Total stroke events	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 vs beta-blockers	4	18135	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]
1.4.2 vs calcium channel blockers	6	35217	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
1.4.3 vs ACE inhibitors	3	30900	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 0.99]
1.4.4 vs alpha adrenergic blockers	2	24396	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.01]
1.4.5 vs angiotensin II receptor blockers	1	655	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [0.12, 70.96]
1.5 Total coronary heart disease	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 vs beta-blockers	4	18135	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.07]
1.5.2 vs calcium channel blockers	6	35217	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
1.5.3 vs ACE inhibitors	3	30900	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.12]
1.5.4 vs alpha adrenergic blockers	2	24396	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.11]
1.5.5 vs angiotensin II receptor blockers	2	1047	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.95]
1.6 Total congestive heart failure	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 vs beta-blockers	1	6569	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.40, 1.19]
1.6.2 vs calcium channel blockers	6	35217	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.66, 0.82]
1.6.3 vs ACE inhibitors	2	30392	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.04]
1.6.4 vs alpha adrenergic blockers	1	24316	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.45, 0.58]
1.7 Withdrawals due to adverse effects	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 vs beta-blockers	5	18501	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.71, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 vs calcium channel blockers	7	33908	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.75, 0.88]
1.7.3 vs ACE inhibitors	3	25254	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.64, 0.84]
1.7.4 vs alpha adrenergic blockers	3	24772	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.54, 0.89]
1.7.5 vs angiotensin II receptor blockers	2	1047	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.91, 4.58]
1.7.6 vs direct renin inhibitors	1	1124	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.88, 2.20]
1.7.7 vs CNS-acting drug	1	366	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.53]

Analysis 1.1. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 1: Total mortality

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 vs beta-blockers						
Berglund 1981	4	53	5	53	1.3%	0.80 [0.23 , 2.82]
HAPPHY 1987	101	3272	96	3297	24.8%	1.06 [0.81 , 1.40]
MRC 1985	128	4297	120	4403	30.7%	1.09 [0.86 , 1.40]
MRC 1992	134	1081	167	1102	42.9%	0.82 [0.66 , 1.01]
VA 1982	1	343	1	340	0.3%	0.99 [0.06 , 15.78]
Subtotal (95% CI)		**9046**		**9195**	**100.0%**	**0.96 [0.84 , 1.10]**
Total events:	368		389			
Heterogeneity: Chi² = 3.87, df = 4 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.1.2 vs calcium channel blockers						
ALLHAT 2000/2002	2203	15255	1256	9048	82.4%	1.04 [0.98 , 1.11]
INSIGHT 2000	172	3164	176	3157	9.2%	0.98 [0.79 , 1.20]
MIDAS 1996	9	441	8	442	0.4%	1.13 [0.44 , 2.90]
NICS-EH 1999	2	210	1	204	0.1%	1.94 [0.18 , 21.26]
SHELL 2003	122	940	145	942	7.6%	0.84 [0.67 , 1.05]
Tresukosol 2005	0	100	1	100	0.1%	0.33 [0.01 , 8.09]
VHAS 1997	4	707	5	707	0.3%	0.80 [0.22 , 2.97]
Subtotal (95% CI)		**20817**		**14600**	**100.0%**	**1.02 [0.96 , 1.08]**
Total events:	2512		1592			
Heterogeneity: Chi² = 4.27, df = 6 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.1.3 vs ACE inhibitors						
ALLHAT 2000/2002	2203	15255	1314	9054	89.4%	1.00 [0.93 , 1.06]
ANBP2 2003	210	3039	195	3044	10.6%	1.08 [0.89 , 1.30]
NESTOR 2004	2	283	1	286	0.1%	2.02 [0.18 , 22.17]
Subtotal (95% CI)		**18577**		**12384**	**100.0%**	**1.00 [0.95 , 1.07]**
Total events:	2415		1510			
Heterogeneity: Chi² = 0.96, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.1.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	851	15255	514	9061	100.0%	0.98 [0.88 , 1.09]
Subtotal (95% CI)		**15255**		**9061**	**100.0%**	**0.98 [0.88 , 1.09]**
Total events:	851		514			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.1.5 vs angiotensin II receptor blockers						
PREVER-treatment 2016	0	333	1	322	100.0%	0.32 [0.01 , 7.88]
Subtotal (95% CI)		**333**		**322**	**100.0%**	**0.32 [0.01 , 7.88]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.1.6 vs direct renin inhibitors						
Schmieder 2009	0	557	1	567	100.0%	0.34 [0.01 , 8.31]
Subtotal (95% CI)		**557**		**567**	**100.0%**	**0.34 [0.01 , 8.31]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						



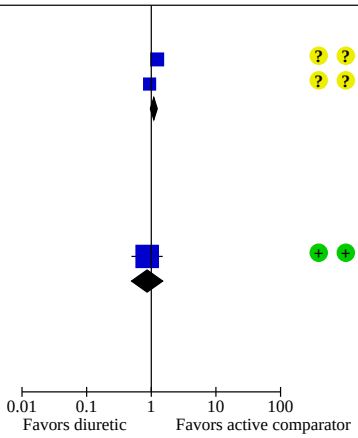


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

Analysis 1.2. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 2: Total serious adverse events

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 vs calcium channel blockers						
INSIGHT 2000	245	3164	198	3157	52.0%	1.23 [1.03 , 1.48]
MIDAS 1996	172	441	183	442	48.0%	0.94 [0.80 , 1.11]
Subtotal (95% CI)		**3605**		**3599**	**100.0%**	**1.09 [0.97 , 1.24]**
Total events:	417		381			
Heterogeneity: Chi² = 5.04, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.2.2 vs direct renin inhibitors						
Schmieder 2009	22	557	26	567	100.0%	0.86 [0.49 , 1.50]
Subtotal (95% CI)		**557**		**567**	**100.0%**	**0.86 [0.49 , 1.50]**
Total events:	22		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						

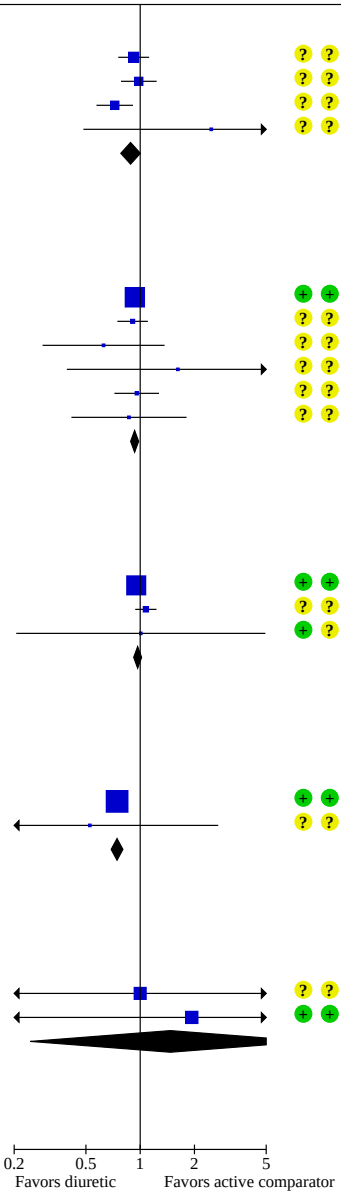


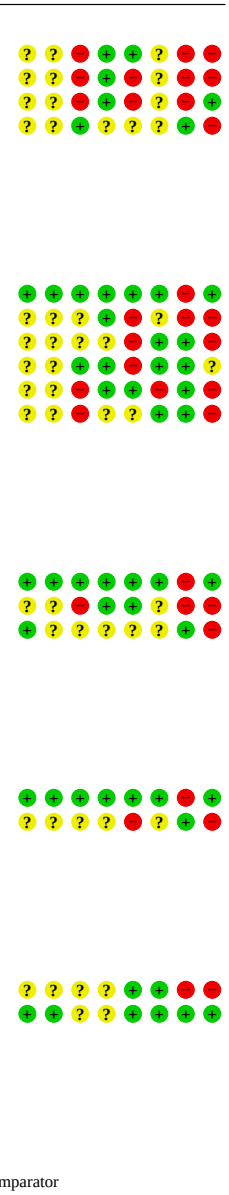
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

Analysis 1.3. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 3: Total cardiovascular events

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 vs beta-blockers						
HAPPHY 1987	179	3272	196	3297	39.8%	0.92 [0.76 , 1.12]
MRC 1985	140	4297	146	4403	29.4%	0.98 [0.78 , 1.23]
MRC 1992 (1)	107	1081	151	1102	30.5%	0.72 [0.57 , 0.91]
VA 1982 (1)	5	343	2	340	0.4%	2.48 [0.48 , 12.69]
Subtotal (95% CI)		**8993**		**9142**	**100.0%**	**0.88 [0.78 , 1.00]**
Total events:	431		495			
Heterogeneity: Chi² = 5.40, df = 3 (P = 0.14); I² = 44%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.3.2 vs calcium channel blockers						
ALLHAT 2000/2002	2761	15255	1753	9048	87.2%	0.93 [0.89 , 0.99]
INSIGHT 2000	182	3164	200	3157	7.9%	0.91 [0.75 , 1.10]
MIDAS 1996	10	441	16	442	0.6%	0.63 [0.29 , 1.37]
NICS-EH 1999	5	210	3	204	0.1%	1.62 [0.39 , 6.69]
SHELL 2003	84	940	88	942	3.5%	0.96 [0.72 , 1.27]
VHAS 1997	13	707	15	707	0.6%	0.87 [0.42 , 1.81]
Subtotal (95% CI)		**20717**		**14500**	**100.0%**	**0.93 [0.89 , 0.98]**
Total events:	3055		2075			
Heterogeneity: Chi² = 1.73, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.3.3 vs ACE inhibitors						
ALLHAT 2000/2002	2761	15255	1724	9054	85.8%	0.95 [0.90 , 1.00]
ANBP2 2003	380	3039	354	3044	14.0%	1.08 [0.94 , 1.23]
PHYLLIS 2004	3	253	3	255	0.1%	1.01 [0.21 , 4.95]
Subtotal (95% CI)		**18547**		**12353**	**100.0%**	**0.97 [0.92 , 1.02]**
Total events:	3144		2081			
Heterogeneity: Chi² = 2.74, df = 2 (P = 0.25); I² = 27%						
Test for overall effect: Z = 1.26 (P = 0.21)						
1.3.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	1379	15255	1100	9061	99.7%	0.74 [0.69 , 0.80]
DAPHNE 2002	2	39	4	41	0.3%	0.53 [0.10 , 2.71]
Subtotal (95% CI)		**15294**		**9102**	**100.0%**	**0.74 [0.69 , 0.80]**
Total events:	1381		1104			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 7.75 (P < 0.00001)						
1.3.5 vs angiotensin II receptor blockers						
ALPINE 2003	1	196	1	196	49.6%	1.00 [0.06 , 15.87]
PREVER-treatment 2016	2	333	1	322	50.4%	1.93 [0.18 , 21.22]
Subtotal (95% CI)		**529**		**518**	**100.0%**	**1.47 [0.25 , 8.79]**
Total events:	3		2			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						





Footnotes

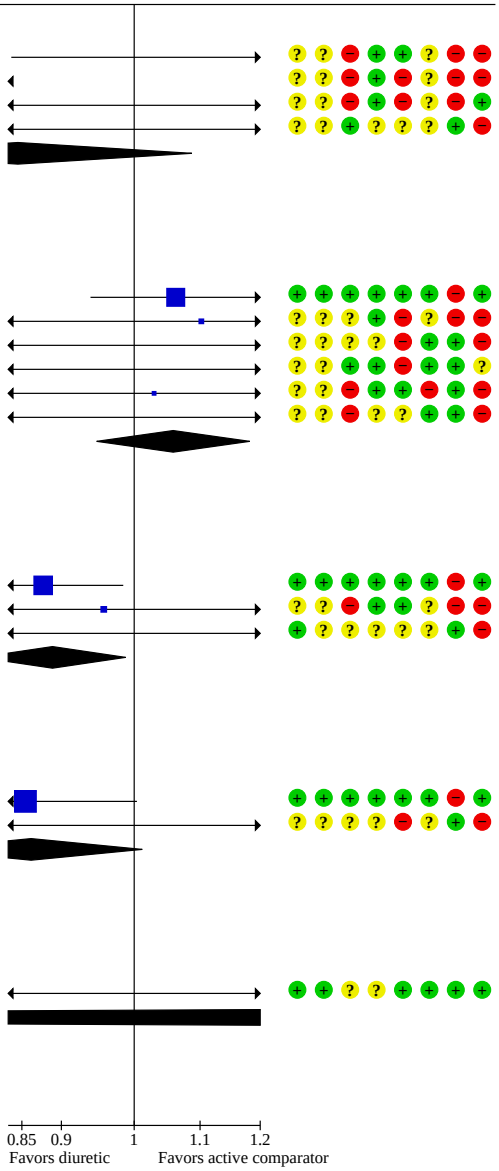
(1) Data checked and accurate.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

Analysis 1.4. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 4: Total stroke events

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 vs beta-blockers						
HAPPHY 1987 (1)	42	3272	32	3297	24.6%	1.32 [0.84 , 2.09]
MRC 1985	18	4297	42	4403	32.1%	0.44 [0.25 , 0.76]
MRC 1992	45	1081	56	1102	42.9%	0.82 [0.56 , 1.20]
VA 1982 (2)	3	343	0	340	0.4%	6.94 [0.36 , 133.83]
Subtotal (95% CI)		**8993**		**9142**	**100.0%**	**0.85 [0.66 , 1.09]**
Total events:	108		130			
Heterogeneity: Chi² = 11.08, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.4.2 vs calcium channel blockers						
ALLHAT 2000/2002	675	15255	377	9048	80.3%	1.06 [0.94 , 1.20]
INSIGHT 2000	74	3164	67	3157	11.4%	1.10 [0.79 , 1.53]
MIDAS 1996	3	441	6	442	1.0%	0.50 [0.13 , 1.99]
NICS-EH 1999	2	210	1	204	0.2%	1.94 [0.18 , 21.26]
SHELL 2003	38	940	37	942	6.3%	1.03 [0.66 , 1.60]
VHAS 1997	4	707	5	707	0.8%	0.80 [0.22 , 2.97]
Subtotal (95% CI)		**20717**		**14500**	**100.0%**	**1.06 [0.95 , 1.18]**
Total events:	796		493			
Heterogeneity: Chi² = 1.63, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.4.3 vs ACE inhibitors						
ALLHAT 2000/2002	675	15255	457	9054	83.5%	0.88 [0.78 , 0.98]
ANBP2 2003	107	3039	112	3044	16.3%	0.96 [0.74 , 1.24]
PHYLLIS 2004	0	253	1	255	0.2%	0.34 [0.01 , 8.21]
Subtotal (95% CI)		**18547**		**12353**	**100.0%**	**0.89 [0.80 , 0.99]**
Total events:	782		570			
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
1.4.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	351	15255	244	9061	99.8%	0.85 [0.73 , 1.00]
DAPHNE 2002	2	39	0	41	0.2%	5.25 [0.26 , 106.01]
Subtotal (95% CI)		**15294**		**9102**	**100.0%**	**0.86 [0.73 , 1.01]**
Total events:	353		244			
Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 29%						
Test for overall effect: Z = 1.82 (P = 0.07)						
1.4.5 vs angiotensin II receptor blockers						
PREVER-treatment 2016	1	333	0	322	100.0%	2.90 [0.12 , 70.96]
Subtotal (95% CI)		**333**		**322**	**100.0%**	**2.90 [0.12 , 70.96]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						



Footnotes

(1) Data checked and accurate

(2) Data checked and accurate.

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

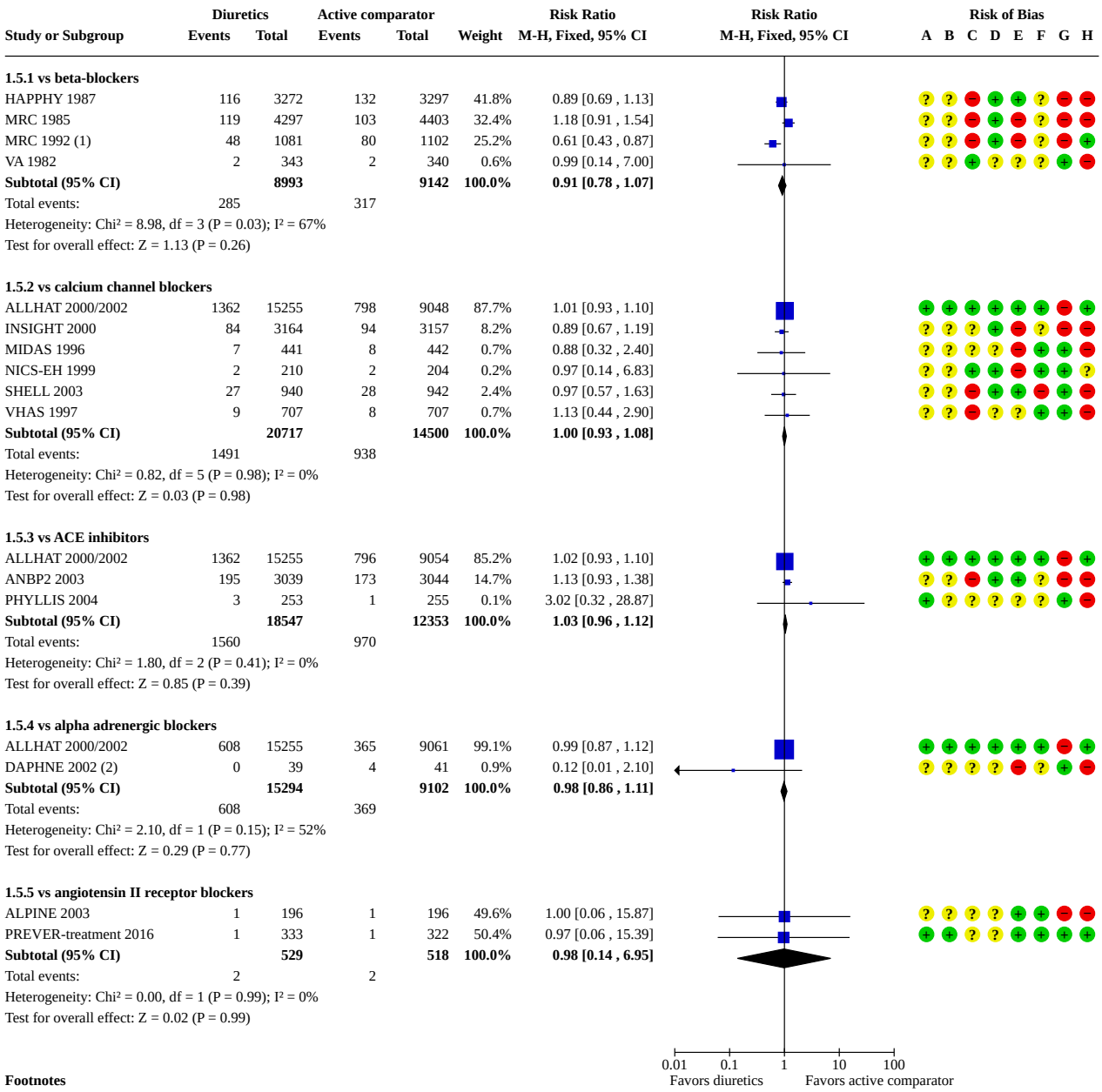
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Use of supplemental drugs

(H) Industry sponsorship

Analysis 1.5. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 5: Total coronary heart disease



Footnotes

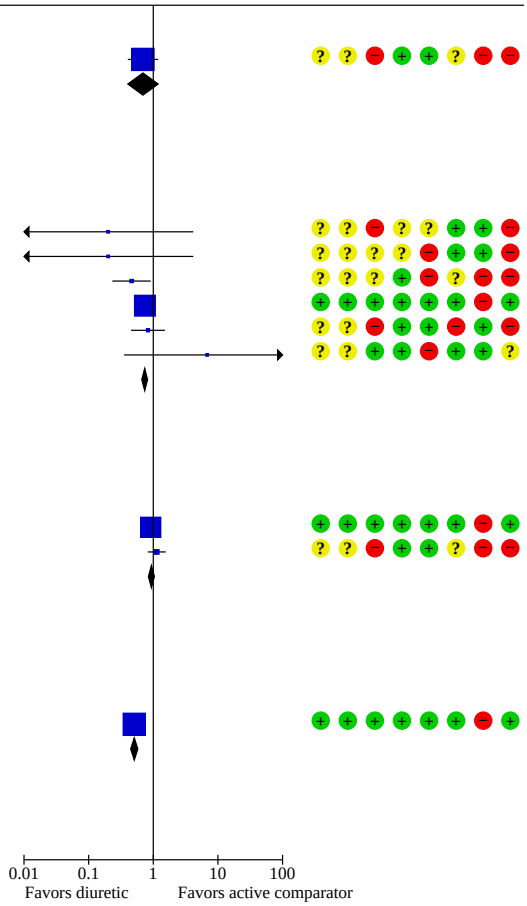
(1) MRC 1992 data are correct.
(2) DAPHNE data are correct

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

Analysis 1.6. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 6: Total congestive heart failure

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 vs beta-blockers						
HAPPHY 1987	22	3272	32	3297	100.0%	0.69 [0.40 , 1.19]
Subtotal (95% CI)		**3272**		**3297**	**100.0%**	**0.69 [0.40 , 1.19]**
Total events:	22		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
1.6.2 vs calcium channel blockers						
VHAS 1997	0	707	2	707	0.3%	0.20 [0.01 , 4.16]
MIDAS 1996	0	441	2	442	0.3%	0.20 [0.01 , 4.16]
INSIGHT 2000	12	3164	26	3157	3.3%	0.46 [0.23 , 0.91]
ALLHAT 2000/2002	724	15255	578	9048	93.0%	0.74 [0.67 , 0.83]
SHELL 2003	19	940	23	942	2.9%	0.83 [0.45 , 1.51]
NICS-EH 1999	3	210	0	204	0.1%	6.80 [0.35 , 130.84]
Subtotal (95% CI)		**20717**		**14500**	**100.0%**	**0.74 [0.66 , 0.82]**
Total events:	758		631			
Heterogeneity: Chi² = 5.58, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 5.82 (P < 0.00001)						
1.6.3 vs ACE inhibitors						
ALLHAT 2000/2002	724	15255	471	9054	89.6%	0.91 [0.81 , 1.02]
ANBP2 2003	78	3039	69	3044	10.4%	1.13 [0.82 , 1.56]
Subtotal (95% CI)		**18294**		**12098**	**100.0%**	**0.94 [0.84 , 1.04]**
Total events:	802		540			
Heterogeneity: Chi² = 1.56, df = 1 (P = 0.21); I² = 36%						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.6.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	420	15255	491	9061	100.0%	0.51 [0.45 , 0.58]
Subtotal (95% CI)		**15255**		**9061**	**100.0%**	**0.51 [0.45 , 0.58]**
Total events:	420		491			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.40 (P < 0.00001)						

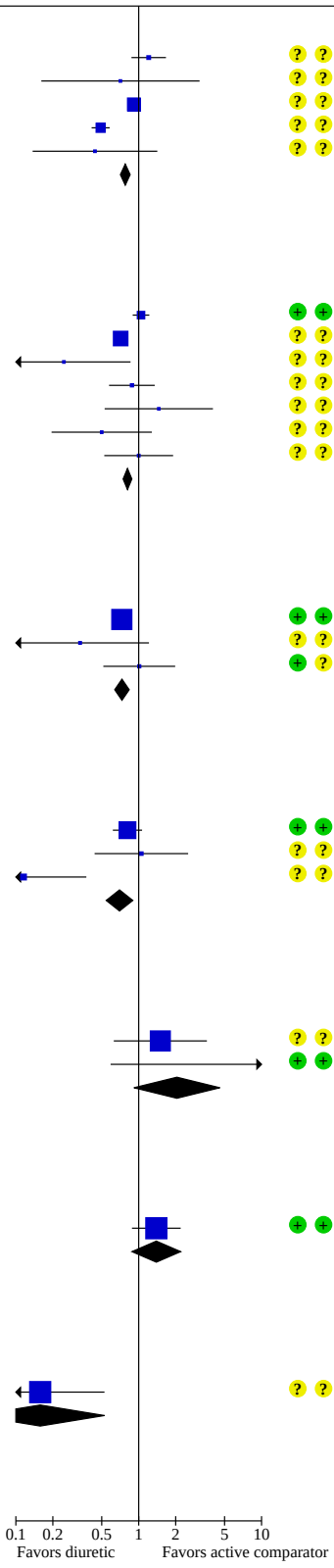


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

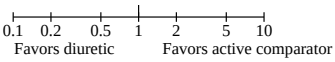
Analysis 1.7. Comparison 1: First-line diuretics versus active comparators: primary outcomes, Outcome 7: Withdrawals due to adverse effects

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 vs beta-blockers						
HAPPHY 1987	79	3272	66	3297	7.1%	1.21 [0.87 , 1.67]
Materson 1993	3	188	4	178	0.4%	0.71 [0.16 , 3.13]
MRC 1985	462	4297	518	4403	55.6%	0.91 [0.81 , 1.03]
MRC 1992	160	1081	333	1102	35.8%	0.49 [0.41 , 0.58]
VA 1982	4	343	9	340	1.0%	0.44 [0.14 , 1.42]
Subtotal (95% CI)		**9181**		**9320**	**100.0%**	**0.78 [0.71 , 0.85]**
Total events:	708		930			
Heterogeneity: Chi² = 43.97, df = 4 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 5.41 (P < 0.00001)						
1.7.2 vs calcium channel blockers						
ALLHAT 2000/2002	426	15255	242	9048	27.2%	1.04 [0.89 , 1.22]
INSIGHT 2000	518	3164	725	3157	64.9%	0.71 [0.64 , 0.79]
Materson 1993	3	188	12	185	1.1%	0.25 [0.07 , 0.86]
MIDAS 1996	36	441	41	442	3.7%	0.88 [0.57 , 1.35]
NICS-EH 1999	9	210	6	204	0.5%	1.46 [0.53 , 4.02]
Tresukosol 2005	6	100	12	100	1.1%	0.50 [0.20 , 1.28]
VHAS 1997	18	707	18	707	1.6%	1.00 [0.52 , 1.91]
Subtotal (95% CI)		**20065**		**13843**	**100.0%**	**0.81 [0.75 , 0.88]**
Total events:	1016		1056			
Heterogeneity: Chi² = 22.67, df = 6 (P = 0.0009); I² = 74%						
Test for overall effect: Z = 5.04 (P < 0.00001)						
1.7.3 vs ACE inhibitors						
ALLHAT 2000/2002	426	15255	347	9054	94.6%	0.73 [0.63 , 0.84]
Materson 1993	3	188	9	188	2.0%	0.33 [0.09 , 1.21]
NESTOR 2004	16	283	16	286	3.5%	1.01 [0.52 , 1.98]
Subtotal (95% CI)		**15726**		**9528**	**100.0%**	**0.73 [0.64 , 0.84]**
Total events:	445		372			
Heterogeneity: Chi² = 2.31, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 4.54 (P < 0.00001)						
1.7.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	120	15255	88	9061	76.6%	0.81 [0.62 , 1.07]
DAPHNE 2002	8	39	8	41	5.4%	1.05 [0.44 , 2.53]
Materson 1993	3	188	26	188	18.0%	0.12 [0.04 , 0.37]
Subtotal (95% CI)		**15482**		**9290**	**100.0%**	**0.70 [0.54 , 0.89]**
Total events:	131		122			
Heterogeneity: Chi² = 10.95, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 2.84 (P = 0.005)						
1.7.5 vs angiotensin II receptor blockers						
ALPINE 2003	12	196	8	196	94.0%	1.50 [0.63 , 3.59]
PREVER-treatment 2016	5	333	0	322	6.0%	10.64 [0.59 , 191.60]
Subtotal (95% CI)		**529**		**518**	**100.0%**	**2.05 [0.91 , 4.58]**
Total events:	17		8			
Heterogeneity: Chi² = 1.74, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.7.6 vs direct renin inhibitors						
Schmieder 2009	41	557	30	567	100.0%	1.39 [0.88 , 2.20]
Subtotal (95% CI)		**557**		**567**	**100.0%**	**1.39 [0.88 , 2.20]**
Total events:	41		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
1.7.7 vs CNS-acting drug						
Materson 1993	3	188	18	178	100.0%	0.16 [0.05 , 0.53]
Subtotal (95% CI)		**188**		**178**	**100.0%**	**0.16 [0.05 , 0.53]**
Total events:	3		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.00 (P = 0.003)						



Risk of bias legend

Analysis 1.7. (Continued)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Use of supplemental drugs
(H) Industry sponsorship

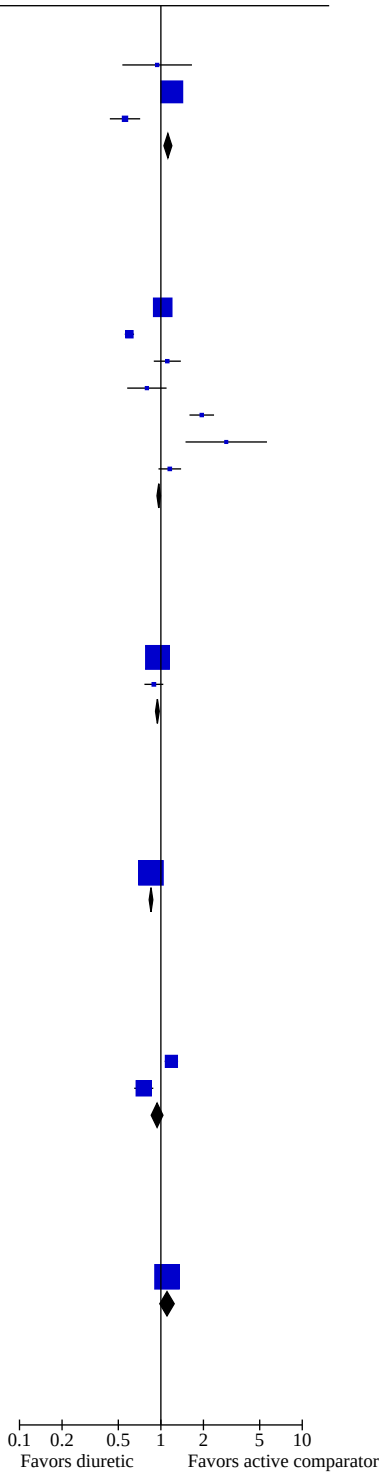
Comparison 2. First-line diuretics versus active comparators: secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Dose titration and addition of second or third drug	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 vs beta-blockers	3	7358	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.05, 1.20]
2.1.2 vs calcium channel blockers	7	35417	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.94, 0.99]
2.1.3 vs ACE inhibitors	2	24878	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.92, 0.97]
2.1.4 vs alpha adrenergic blockers	1	24316	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.83, 0.88]
2.1.5 vs angiotensin II receptor blockers	2	1047	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.03]
2.1.6 vs direct renin inhibitors	1	1124	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.98, 1.24]
2.2 Switching to other antihypertensive therapies	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 vs beta-blockers	1	106	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.53, 7.58]
2.2.2 vs calcium channel blockers	2	2297	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.18]
2.2.3 vs alpha adrenergic blockers	2	24396	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.09, 0.12]
2.3 Systolic blood pressure at 1 year	19		Mean Difference (IV, Fixed, 99% CI)	Subtotals only
2.3.1 vs beta-blockers	5	18241	Mean Difference (IV, Fixed, 99% CI)	-2.94 [-3.58, -2.29]
2.3.2 vs calcium channel blockers	7	31585	Mean Difference (IV, Fixed, 99% CI)	-1.36 [-1.80, -0.92]
2.3.3 vs ACE inhibitors	4	27289	Mean Difference (IV, Fixed, 99% CI)	-2.39 [-2.93, -1.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.4 vs alpha adrenergic blockers	2	18781	Mean Difference (IV, Fixed, 99% CI)	-3.01 [-3.65, -2.37]
2.3.5 vs angiotensin II receptor blockers	2	1047	Mean Difference (IV, Fixed, 99% CI)	-1.93 [-4.32, 0.47]
2.3.6 vs direct renin inhibitors	1	1124	Mean Difference (IV, Fixed, 99% CI)	0.90 [-1.30, 3.10]
2.4 Diastolic blood pressure at 1 year	19		Mean Difference (IV, Fixed, 99% CI)	Subtotals only
2.4.1 vs beta-blockers	5	18241	Mean Difference (IV, Fixed, 99% CI)	-0.29 [-0.65, 0.07]
2.4.2 vs calcium channel blockers	7	31585	Mean Difference (IV, Fixed, 99% CI)	0.47 [0.20, 0.73]
2.4.3 vs ACE inhibitors	4	27391	Mean Difference (IV, Fixed, 99% CI)	-0.37 [-0.67, -0.07]
2.4.4 vs alpha adrenergic blockers	2	18781	Mean Difference (IV, Fixed, 99% CI)	0.00 [-0.38, 0.38]
2.4.5 vs angiotensin II receptor blockers	2	1047	Mean Difference (IV, Fixed, 99% CI)	0.04 [-1.21, 1.29]
2.4.6 vs direct renin inhibitors	1	1124	Mean Difference (IV, Fixed, 99% CI)	1.00 [-0.44, 2.44]

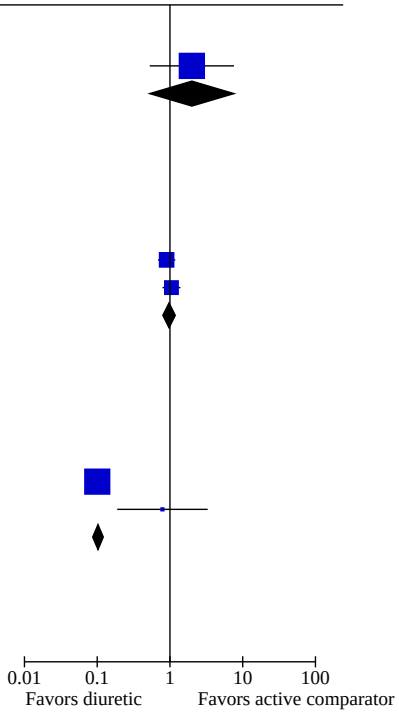
Analysis 2.1. Comparison 2: First-line diuretics versus active comparators: secondary outcomes, Outcome 1: Dose titration and addition of second or third drug

Study or Subgroup	Diuretics Events	Diuretics Total	Active comparator Events	Active comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 vs beta-blockers						
Berglund 1981	16	53	17	53	1.5%	0.94 [0.53 , 1.66]
HAPPHY 1987	1221	3272	1030	3297	87.6%	1.19 [1.12 , 1.28]
VA 1982	72	343	128	340	11.0%	0.56 [0.44 , 0.71]
Subtotal (95% CI)		**3668**		**3690**	**100.0%**	**1.12 [1.05 , 1.20]**
Total events:	1309		1175			
Heterogeneity: Chi² = 34.56, df = 2 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 3.48 (P = 0.0005)						
2.1.2 vs calcium channel blockers						
ALLHAT 2000/2002	6209	15255	3574	9048	72.2%	1.03 [1.00 , 1.06]
INSIGHT 2000	756	3164	1259	3157	20.3%	0.60 [0.56 , 0.65]
MIDAS 1996	123	441	111	442	1.8%	1.11 [0.89 , 1.38]
NICS-EH 1999	50	210	61	204	1.0%	0.80 [0.58 , 1.10]
SHELL 2003	235	940	121	942	1.9%	1.95 [1.59 , 2.38]
Tresukosol 2005	29	100	10	100	0.2%	2.90 [1.49 , 5.63]
VHAS 1997	185	707	160	707	2.6%	1.16 [0.96 , 1.39]
Subtotal (95% CI)		**20817**		**14600**	**100.0%**	**0.97 [0.94 , 0.99]**
Total events:	7587		5296			
Heterogeneity: Chi² = 233.82, df = 6 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 2.39 (P = 0.02)						
2.1.3 vs ACE inhibitors						
ALLHAT 2000/2002	6209	15255	3893	9054	96.8%	0.95 [0.92 , 0.98]
NESTOR 2004	143	283	162	286	3.2%	0.89 [0.77 , 1.04]
Subtotal (95% CI)		**15538**		**9340**	**100.0%**	**0.94 [0.92 , 0.97]**
Total events:	6352		4055			
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
2.1.4 vs alpha adrenergic blockers						
ALLHAT 2000/2002	6107	15255	4261	9061	100.0%	0.85 [0.83 , 0.88]
Subtotal (95% CI)		**15255**		**9061**	**100.0%**	**0.85 [0.83 , 0.88]**
Total events:	6107		4261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.79 (P < 0.00001)						
2.1.5 vs angiotensin II receptor blockers						
ALPINE 2003	165	196	139	196	42.6%	1.19 [1.07 , 1.32]
PREVER-treatment 2016	144	333	184	322	57.4%	0.76 [0.65 , 0.88]
Subtotal (95% CI)		**529**		**518**	**100.0%**	**0.94 [0.85 , 1.03]**
Total events:	309		323			
Heterogeneity: Chi² = 25.33, df = 1 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 1.27 (P = 0.20)						
2.1.6 vs direct renin inhibitors						
Schmieder 2009	292	557	269	567	100.0%	1.10 [0.98 , 1.24]
Subtotal (95% CI)		**557**		**567**	**100.0%**	**1.10 [0.98 , 1.24]**
Total events:	292		269			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						



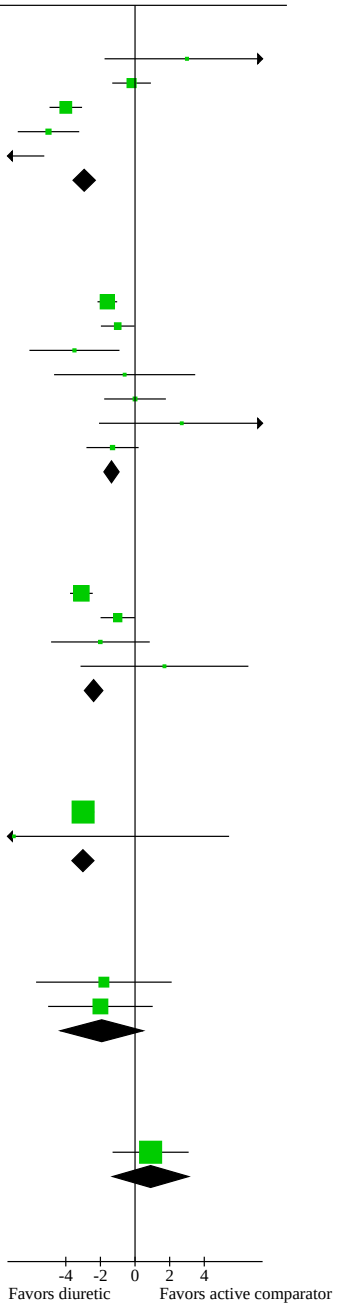
Analysis 2.2. Comparison 2: First-line diuretics versus active comparators: secondary outcomes, Outcome 2: Switching to other antihypertensive therapies

Study or Subgroup	Diuretics Events	Total	Active comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 vs beta-blockers						
Berglund 1981	6	53	3	53	100.0%	2.00 [0.53 , 7.58]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**2.00 [0.53 , 7.58]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.2.2 vs calcium channel blockers						
MIDAS 1996	79	441	88	442	51.7%	0.90 [0.68 , 1.18]
VHAS 1997	86	707	82	707	48.3%	1.05 [0.79 , 1.39]
Subtotal (95% CI)		**1148**		**1149**	**100.0%**	**0.97 [0.80 , 1.18]**
Total events:	165		170			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.78)						
2.2.3 vs alpha adrenergic blockers						
ALLHAT 2000/2002	153	15255	907	9061	99.7%	0.10 [0.08 , 0.12]
DAPHNE 2002	3	39	4	41	0.3%	0.79 [0.19 , 3.30]
Subtotal (95% CI)		**15294**		**9102**	**100.0%**	**0.10 [0.09 , 0.12]**
Total events:	156		911			
Heterogeneity: Chi² = 7.87, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 26.67 (P < 0.00001)						



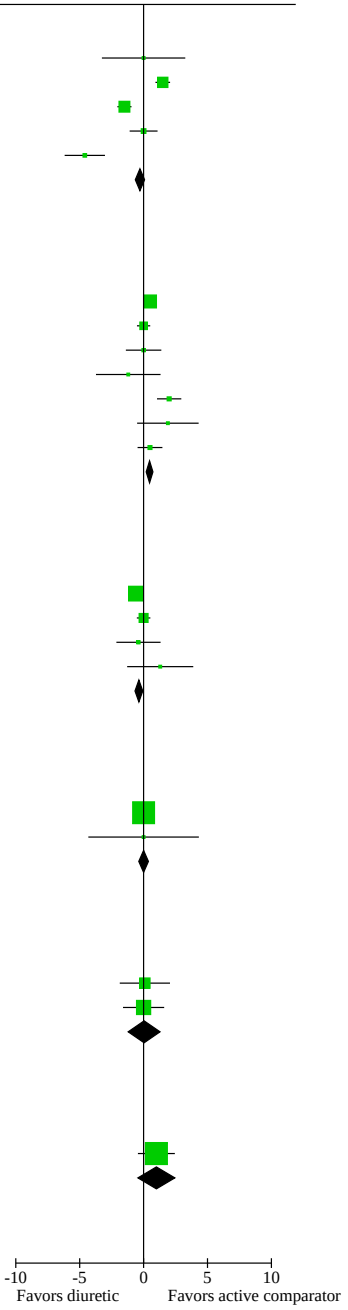
Analysis 2.3. Comparison 2: First-line diuretics versus active comparators: secondary outcomes, Outcome 3: Systolic blood pressure at 1 year

Study or Subgroup	Diuretics Mean	SD	Total	Active comparator Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
2.3.1 vs beta-blockers								
Berglund 1981	129	9	53	126	10	53	1.8%	3.00 [-1.76 , 7.76]
HAPPHY 1987	140.8	16	3272	141	19	3297	33.3%	-0.20 [-1.32 , 0.92]
MRC 1985	-13	17	4297	-9	17	4403	47.0%	-4.00 [-4.94 , -3.06]
MRC 1992	151	16.1	1081	156	16.1	1102	13.2%	-5.00 [-6.78 , -3.22]
VA 1982	129	15	343	137.2	15	340	4.7%	-8.20 [-11.16 , -5.24]
Subtotal (99% CI)			**9046**			**9195**	**100.0%**	**-2.94 [-3.58 , -2.29]**
Heterogeneity: Chi² = 88.71, df = 4 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 11.76 (P < 0.00001)								
2.3.2 vs calcium channel blockers								
ALLHAT 2000/2002	136.9	15.8	12862	138.5	14.9	7609	60.0%	-1.60 [-2.17 , -1.03]
INSIGHT 2000	139	15	3164	140	15	3157	20.5%	-1.00 [-1.97 , -0.03]
MIDAS 1996	-19.5	15	441	-16	15	442	2.9%	-3.50 [-6.10 , -0.90]
NICS-EH 1999	147.4	16.4	210	148	15.8	204	1.2%	-0.60 [-4.68 , 3.48]
SHELL 2003	144	15	940	144	15	942	6.1%	0.00 [-1.78 , 1.78]
Tresukosol 2005	147.8	12.3	100	145.1	13.9	100	0.8%	2.70 [-2.08 , 7.48]
VHAS 1997	140.2	11	707	141.5	11	707	8.5%	-1.30 [-2.81 , 0.21]
Subtotal (99% CI)			**18424**			**13161**	**100.0%**	**-1.36 [-1.80 , -0.92]**
Heterogeneity: Chi² = 15.48, df = 6 (P = 0.02); I² = 61%								
Test for overall effect: Z = 7.97 (P < 0.00001)								
2.3.3 vs ACE inhibitors								
ALLHAT 2000/2002	136.9	15.8	12862	140	18.5	7521	66.2%	-3.10 [-3.76 , -2.44]
ANBP2 2003	146	15	3039	147	15	3044	29.1%	-1.00 [-1.99 , -0.01]
NESTOR 2004	137.3	12	283	139.3	14.3	286	3.5%	-2.00 [-4.85 , 0.85]
PHYLLIS 2004	141.3	15	127	139.6	15	127	1.2%	1.70 [-3.15 , 6.55]
Subtotal (99% CI)			**16311**			**10978**	**100.0%**	**-2.39 [-2.93 , -1.86]**
Heterogeneity: Chi² = 25.67, df = 3 (P < 0.0001); I² = 88%								
Test for overall effect: Z = 11.54 (P < 0.00001)								
2.3.4 vs alpha adrenergic blockers								
ALLHAT 2000/2002	137	15	11902	140	17	6799	99.7%	-3.00 [-3.64 , -2.36]
DAPHNE 2002	148	19	39	155	24	41	0.3%	-7.00 [-19.43 , 5.43]
Subtotal (99% CI)			**11941**			**6840**	**100.0%**	**-3.01 [-3.65 , -2.37]**
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%								
Test for overall effect: Z = 12.16 (P < 0.00001)								
2.3.5 vs angiotensin II receptor blockers								
ALPINE 2003	-22.8	14.9	196	-21	15.2	196	37.3%	-1.80 [-5.72 , 2.12]
PREVER-treatment 2016	128	15	333	130	15	322	62.7%	-2.00 [-5.02 , 1.02]
Subtotal (99% CI)			**529**			**518**	**100.0%**	**-1.93 [-4.32 , 0.47]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 2.07 (P = 0.04)								
2.3.6 vs direct renin inhibitors								
Schmieder 2009	-21.2	14.3	557	-22.1	14.3	567	100.0%	0.90 [-1.30 , 3.10]
Subtotal (99% CI)			**557**			**567**	**100.0%**	**0.90 [-1.30 , 3.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
Test for subgroup differences: Chi² = 0.00, df = 5 (P < 0.00001), I² = 0%								



Analysis 2.4. Comparison 2: First-line diuretics versus active comparators: secondary outcomes, Outcome 4: Diastolic blood pressure at 1 year

Study or Subgroup	Diuretics Mean	SD	Total	Active comparator Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
2.4.1 vs beta-blockers								
Berglund 1981	95	6	53	95	7	53	1.2%	0.00 [-3.26 , 3.26]
HAPPHY 1987	90.5	8.5	3272	89	9.5	3297	39.8%	1.50 [0.93 , 2.07]
MRC 1985	-5.5	10	4297	-4	10	4403	42.8%	-1.50 [-2.05 , -0.95]
MRC 1992	79	9.9	1081	79	9.9	1102	11.0%	0.00 [-1.09 , 1.09]
VA 1982	88.2	8	343	92.8	8	340	5.2%	-4.60 [-6.18 , -3.02]
Subtotal (99% CI)			**9046**			**9195**	**100.0%**	**-0.29 [-0.65 , 0.07]**
Heterogeneity: Chi² = 146.71, df = 4 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 2.04 (P = 0.04)								
2.4.2 vs calcium channel blockers								
ALLHAT 2000/2002	79.2	9.9	12862	78.7	9.5	7609	53.4%	0.50 [0.14 , 0.86]
INSIGHT 2000	83	8	3164	83	8	3157	25.7%	0.00 [-0.52 , 0.52]
MIDAS 1996	-13	8	441	-13	8	442	3.6%	0.00 [-1.39 , 1.39]
NICS-EH 1999	78.9	9.4	210	80.1	10.5	204	1.1%	-1.20 [-3.73 , 1.33]
SHELL 2003	87	8	940	85	8	942	7.7%	2.00 [1.05 , 2.95]
Tresukosol 2005	76.1	7.4	100	74.2	5.7	100	1.2%	1.90 [-0.51 , 4.31]
VHAS 1997	85.7	8.1	707	85.2	5.9	707	7.3%	0.50 [-0.47 , 1.47]
Subtotal (99% CI)			**18424**			**13161**	**100.0%**	**0.47 [0.20 , 0.73]**
Heterogeneity: Chi² = 28.72, df = 6 (P < 0.0001); I² = 79%								
Test for overall effect: Z = 4.57 (P < 0.00001)								
2.4.3 vs ACE inhibitors								
ALLHAT 2000/2002	79.3	9.9	12962	79.9	10.5	7523	62.5%	-0.60 [-0.98 , -0.22]
ANBP2 2003	82	8	3039	82	8	3044	33.0%	0.00 [-0.53 , 0.53]
NESTOR 2004	81	8.1	283	81.4	7.9	286	3.1%	-0.40 [-2.13 , 1.33]
PHYLLIS 2004	86.5	8	127	85.2	8	127	1.4%	1.30 [-1.29 , 3.89]
Subtotal (99% CI)			**16411**			**10980**	**100.0%**	**-0.37 [-0.67 , -0.07]**
Heterogeneity: Chi² = 8.40, df = 3 (P = 0.04); I² = 64%								
Test for overall effect: Z = 3.14 (P = 0.002)								
2.4.4 vs alpha adrenergic blockers								
ALLHAT 2000/2002	79	9	11902	79	10	6799	99.2%	0.00 [-0.38 , 0.38]
DAPHNE 2002	87	7	39	87	8	41	0.8%	0.00 [-4.32 , 4.32]
Subtotal (99% CI)			**11941**			**6840**	**100.0%**	**0.00 [-0.38 , 0.38]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
2.4.5 vs angiotensin II receptor blockers								
ALPINE 2003	-12.9	7.7	196	-13	7.4	196	40.2%	0.10 [-1.86 , 2.06]
PREVER-treatment 2016	82	8	333	82	8	322	59.8%	0.00 [-1.61 , 1.61]
Subtotal (99% CI)			**529**			**518**	**100.0%**	**0.04 [-1.21 , 1.29]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.08 (P = 0.93)								
2.4.6 vs direct renin inhibitors								
Schmieder 2009	-15	9.4	557	-16	9.4	567	100.0%	1.00 [-0.44 , 2.44]
Subtotal (99% CI)			**557**			**567**	**100.0%**	**1.00 [-0.44 , 2.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.78 (P = 0.07)								
Test for subgroup differences: Chi² = 0.00, df = 5 (P < 0.00001), I² = 0%								



APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 24, 2021>
Search Date: 25 March 2021

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1 exp thiazides/
2 exp sodium chloride symporter inhibitors/
3 exp sodium potassium chloride symporter inhibitors/
4 thiazide*.tw,kf.
5 ((sodium chloride adj2 cotransporter inhibit*) or (sodium chloride adj2 co-transporter inhibit*) or (sodium chloride adj2 symporter inhibit*)).tw,kf.
6 ((ceiling adj2 diuretic*) or (loop adj2 diuretic*) or (potassium-depleting adj2 diuretic*)).tw,kf.
7 (amiloride or amiclaran or amidal or amiduret trom or amikal or "amilo 5" or amiloberag or amilorid or amiloridehydrochlorhydrate or amiloridine or amipramidine or amyloride or arumil or berkamil or colectril or guanamprazine or kaluril or medamor or midamor or midoride or "mk 870" or modamide or nirulid or pandiuren).mp.
8 (azosemide or azosemid or luret or "ple 1053" or "sk 110").mp.
9 (bendroflumethiazide or aprinox or bendrofluazide or bendroflumethiazide or benzhydroflumethiazide or benzydroflumethiazide or benzyl hydroflumethiazide or benzylhydroflumethiazide or benzide or berkozide or bristuron or centonuron or centyl or esberizid or naturetin or naturine or neo naclex or neonaclex or naturetin or naturine or neonadex or pluryl or pluryle or repicin or salures or sinesalin or urizid).mp.
10 (bumetanide or budema or bumedyl or bumelex or bumet or bumetamide or bumethanide or bumetidine or bumex or burinax or burinex or busix or butinat or butinon or bymex or cambiex or drenural or farmadiuril or fontego or fordiuran or lixil or lunetoron or miccil or "pf 1593" or "pf-1593" or pf1593 or primex or "ro 10 6338" or "ro 10-6338" or "ro10 6338" or ro10-6338).mp.
11 (butizide or buthiazide or eunephran or eunepran or isobutylhydrochlorothiazide or modenol or saltucin or thiabulazid or thiabutazide or thiobulazid or tiabutazide).mp.
12 (chlorothiazide or chlorosal or chlorothiazid or chlorothiazidum or chlorothiazine or chlorthiazide or chlotride or diachlor or diuril or diurilix or diuriwas wassermann milano or flumen or lyovac or saluric or warduzuide).mp.
13 (chlorthalidone or aquadon or chlorphthalidolone or chlortalidon or chlortalidone or clortalidone or chlorthalidine or chlorthalidon or chlorthialidone or clortalil or edemdal or hidronal or higroton or higrotona or hygroton or hylidone or hypertol or hythalton or igrolina or igroton or isoren or natriuran or oxodolin or oxodoline or phthalamidine or phthalamodine or phthalamudine or renon or servidone or thalitone or urandil or urofinil or zambesil).mp.
14 (cicletanine or "bn 1270" or "bn 50417" or "bn 50418" or bn1270 or bn50417 or bn50418 or cicletanide or cycletanide or justar or tenstaten or tenstatin).mp.
15 (clopamide or adurix or aquez or brinaldix or brinaldrix or brinedine or chlosudimeprimylum clopamid or clopamidum or clopamine).mp.
16 (clorexone or chlorexolone or flonatril or klorex or nefrolan or cyclothizaide or anhydron or doburil or fluidil or valmiran).mp.
17 (cyclopenthiazide or cyclomethiazide or cyclopenthiazine or cyclopentiazide or navidex or navidrex or navidrix or salimid or tsiklometiazid).mp.
18 (diapamide or thiamizide or tiamizide or fenquizone or idrolone).mp.
19 (eplerenone or "cgp 30 083" or "cgp 30083" or cgp30083 or elecor or eplerenon or epoxymexrenone or inspra or "sc 66110" or sc66110).mp.
20 (ethacrynic acid or edecril or edecrin or edecrina or endecril or etacrinic acid or etacrynate or etacrynic acid or ethacrinic acid or ethacrynate or ethacryonic acid or ethocrynic acid or ethycrynic acid or hydromedin or lyovac sodium edecrin or "mk 595" or "nsc 85791" or reomax or sodium ethacrynate or uregit or uregyt).mp.
21 (etozolin or elkapin or etazolin or etozoline or "go 687" or go687 or "goe 687" or goe687 or ozolinone ethyl ester or "w 2900" or w2900).mp.
22 (furosemide or aldic or aluzine or anfuramaide or aquarid or arasemide or cetasix or desal or diamazon or dirine or discoid or diumide or diural or diuresal or diurin or diurix or diurolasa or diusemide or diuspec or dryptal or durafurid or edenol or errolon or eutensin or eutensine or flurosemide or franyl or fretic or frumid or frusedan or frusehexal or frusema or frusemidor frusemide or frusid or fruzex or fumarenid or fumide or furanthril or furantral or furantril or furanturil or furasemide or furesin or furesis or furetic or furix or furmid or furo puren or furo-basan or furo-puren or furobasan or furomen or furomex or furomide or furomin or furopuren or furorese or furosamide or furoscan or furose or furosemid or furosemix or furosimide or furosix or furovite or fursemide or fusid or fusimex or hissuflux or hydro rapid or impugan or jufurix or kofuzon or kutrix or lasiletten or lasilix or lasix or laxis or laxur or "lb 502" or lb502 or luramide or marsemide or mirfat or odemase or odemex or oedemase or oedemex or pharmix or promedes or radisemide or rasitol or retep or salinex or seguril or selectofur or sigasalur or uremide or uresix or urex-m or vesix or zafurida).mp.
23 (hydrochlorothiazide or apo-hydro or aquarius or aquazide or bisalunil or bpzide or bremil or chlorosulthiadil or chlorsulfonamidodihydrobenzothiadiazine or cidrex or clothia or dehydratin or diaqua or dichlorosal or dichlothiazide or dichlotride or dichlozid or diclotride or didralin or dihydrochlorothiazide or dihydrodiuril or direma or disaluril or disothiazide or dithiazide or diu melusin or diumelusin or diurace or diurex or esidrex or esidrix or fluvin or hctz or hidrenox or hidril or hidroronol or hidrosaluretil or hudorex or hychlozide or hydrex-semi or hydril or hydro aquil or hydrochlor or hydrochloro thiazide or hydrochlorothiamide or hydrochlorothiazid or hydrochlorothiazine or hydrochlorzide or hydrochlothiazide or hydro diuril or hydrodiuril or hydromal or hydrororonol or hydro saluric or hydrosaluric or hydrothide or hydro tonuron or hydrozide or hypothiazid or hypothiazide or ivaugan or maschitt or microzide or mictrin or nefrix or neoflumen or newtolide or niagar or oretic or pantemon or ridaq or sectrazide or tandiur or thiadril or thiaretic or thiuretic or urodiazin or urodiazine or urozide or vetidrex).mp.
24 (hydroflumethiazide or bristab or di ademil or diademil or dihydroflumethiazide or diraudixin or diucardin or hiserpin or hydrenox or leodrin or leodrine or metflorylthiadiazine or naclex or rontyl or saluron or sisuril or trifluoromethylhydrothiazide).mp.

25 (indapamide or agelan or apadex or arifon or damide or dapamax or diflerix or dixamid or extur or fludex or fluidema or frumeron or indahexal or indalix or indamol or indapam or indapress or indicontin or indoline or indopamide or inpamide or insig or ipamix or lorvas or loxide or lozol or metindamide or millibar or naplin or natrilix or natrix or noranat or pamid or pressural or pretanix or rinalix or sicco or tandix or tertensif or veroxil).mp.
26 (indacrinone or indacrinic acid or indacrynic acid or "mk 196").mp.
27 (mefruside or bay caron or bay1500 or baycaron or baycarone or mefrusid).mp.
28 (metolazone or barolyn or diulo or metalazone or metenix or metolazon or miclox or microx or mykrox or normelan or xuret or zaroxolyn).mp.
29 (methylclothiazide or aquatensen or enduron or enduron-m or enduronum or methyclothiazide or methylchlorothiazide or thiazidil).mp.
30 (muzolimine or "bay g 2821" or "bay g2821" or "bayer g 2821" or "bayer g2821" or edrul or musolimino).mp.
31 (ozolinone or "go 3282" or go3282 or "goe 3282" or goe3282 or "goedecke 3282").mp.
32 phenoxybenzoic acid.mp.
33 (piretanide or arelix or arlix or eurelix or "hoe 118" or hoe118 or lafax or perbilen or "s 73 4118" or "s 734118" or s734118 or tauliz).mp.
34 (polythiazide or drenusil or nephril or polythiazide or renese).mp.
35 (quinethazone or aquamox or chinethazon or chinethazone or guinethazone or hydromox or kinetazone or quinethazon).mp.
36 (spironolactone or abbolactone or acelat or adultmin or alaton or alatone or aldace or aldactone or aldopur or aldospirone or almatol or aquareduct or berlactone or carospir or "crl 635" or crl635 or diram or duraspiron or "dyta urese" or dytaurese or espironolactona or flumach or frumikal or jenaspiron or hypazon or idrolattone or merabis or "novo spiroton" or "novo-spiriton" or novospiroton or osiren or osyrol or pirolacton or pondactone or practon or prilactone or resacton or "sas 1060" or sas1060 or "sc 9420" or "sc-9420" or sc9420 or spiractin or spiridon or spirix or spirobeta or "spiro ct" or spiroctan or spirogamma or spirohexal or spirolacton or spirolactone or spirolang or "spiro l.u.t." or spiron or spirone or spironex or spirono isis or spironol or spironolacton or spironolakton or spironone or spirospare or spirothiobarbiturate or spirotone or spiro von ct or supra puren or suprapuren or uractone or veroshpiron or verospiron or verospirone or xenalon or youlactone).mp.
37 (ticrynafen or "anp 3624" or "anp-3624" or anp3624 or diflurex or selacryn or "skf 62698" or "skf-62698" or skf62698 or selacryn or thienilic acid or thienylic acid or tienilic acid).mp.
38 tizolemide.mp.
39 (torsemide or "bm 02015" or "bm 2015" or bm02015 or bm2015 or demadex or diuremid or "jdl 464" or jdl464 or luprac or presaril or toradiur or torem or torrem or torasemide or unat or upcard).mp.
40 (triamterene or dyrenium or dytac or urocaudal or ademin or ademine or dyren or dyrenium or dytac or iatropur or jatropur or noridyl or "nsc 77625" or nsc77625 or pterofen or pterophene or "sk and f 8542" or "skf 8542" or skf8542 or teriam or triampterene or triamterence or triamterens or triamteril or triteren or uretren or urocaudal).mp.
41 (trichloromethiazide or aquazide or dichloromethylhydrochlorothiazide or diurese or esmarin or eurinol or fluitran or flutra or gangesol or hydrotrichlorothiazide or metahydrin or methahydrin or naqua or naquasone or salurin or triazide or trichlordiuride or trichlorex or trichlormethazide or trichlormethiazide or trichlormas or trichloromethylhydrochlorothiazide or triflumen or wadel).mp.
42 (tripamide or "adr 033" or adr033 or "e 614" or e614 or normonal).mp.
43 (xipamide or aquaforil or aquaphor or aquaphoril or aquavor or "bei 1293" or diurexan or lumitens or xipamid or xypamide or zipix).mp.
44 or/1-43
45 exp angiotensin-converting enzyme inhibitors/
46 angiotensin converting enzyme inhibit*.tw,kf.
47 (ace adj2 inhibit*).tw,kf.
48 acei.tw,kf.
49 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw,kf.
50 or/45-49
51 exp Angiotensin Receptor Antagonists/
52 (angiotensin adj3 receptor antagon*).tw,kf.
53 (angiotensin adj3 receptor block*).tw,kf.
54 (arb or arbs).tw,kf.
55 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw,kf.
56 or/51-55
57 exp calcium channel blockers/
58 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw,kf.

59 (calcium adj2 (antagonist* or block* or inhibit*)).tw,kf.
60 or/57-59
61 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.
62 (reserpine or serpentina or rauwolfia or serpasil).mp.
63 (clonidine or adesipress or arkamin or caprysin or catapres* or catasan or chlofazolin or chlophazolin or clinidine or clofelin* or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin* or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.
64 exp hydralazine/
65 (hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).mp.
66 or/61-65
67 exp adrenergic beta-antagonists/
68 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw,kf.
69 (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).tw,kf.
70 or/67-69
71 exp adrenergic alpha antagonists/
72 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw,kf.
73 (adrenergic adj2 (alpha or antagonist*)).tw,kf.
74 ((adrenergic or alpha or receptor*) adj2 block*).tw,kf.
75 or/71-74
76 50 or 56 or 60 or 66 or 70 or 75
77 hypertension/
78 essential hypertension/
79 (antihypertens* or hypertens*).tw,kf.
80 ((elevat* adj2 arterial pressur*) or (elevat* adj2 blood pressur*) or (elevat* adj2 diastolic pressur*) or (elevat* adj2 systolic pressur*)).tw,kf.
81 ((high adj2 arterial pressur*) or (high adj2 blood pressur*) or (high adj2 diastolic pressure) or (high adj2 systolic pressur*)).tw,kf.
82 ((rais* adj2 arterial pressur*) or (rais* adj2 blood pressur*) or (rais* adj2 diastolic pressure) or (rais* adj2 systolic pressur*)).tw,kf.
83 ((elevat* adj2 bp) or (elevat* adj2 dbp) or (elevat* adj2 sbp)).tw,kf.
84 ((high adj2 bp) or (high adj2 dbp) or (high adj2 sbp)).tw,kf.
85 ((rais* adj2 bp) or (rais* adj2 dbp) or (rais* adj2 sbp)).tw,kf.
86 or/77-85
87 randomized controlled trial.pt.
88 controlled clinical trial.pt.
89 randomi*ed.ab.
90 placebo.ab.
91 dt.fs.
92 randomly.ab.
93 trial.ab.
94 groups.ab.
95 or/87-94
96 animals/ not (humans/ and animals/)
97 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/
98 (pregnancy-induced or ocular hypertens* or preeclampsia or pre-eclampsia).ti.
99 95 not (96 or 97 or 98)
100 44 and 76 and 86 and 99

Database: Cochrane Hypertension Specialized Register via Cochrane Register of Studies

Search Date: 27 June 2022

#1 thiazide* AND INREGISTER
#2 (sodium chloride) NEAR2 (cotransporter inhibit* OR co-transporter inhibit* OR symporter inhibit*) AND INREGISTER
#3 (ceiling OR loop OR potassium-depleting) NEAR2 (diuretic) AND INREGISTER
#4 (amiloride OR amiclaran OR amidal OR amiduret trom OR amikal OR "amilo 5" OR amiloberag OR amilorid OR amiloridehydrochlorhydrate OR amiloridine OR amipramidine OR amyloride OR arumil OR berkamil OR colectril OR guanamprazine OR kaluril OR medamor OR midamor OR midoride OR "mk 870" OR modamide OR nirulid OR pandiuren) AND INREGISTER
#5 (azosemide OR azosemid OR luret) AND INREGISTER
#6 (bendroflumethiazide OR aprinox OR bendrofluazide OR bendroflumethiazide OR benzhydroflumethiazide OR benzydroflumethiazide OR benzyl hydroflumethiazide OR benzylhydroflumethiazide OR benzide OR berkozide OR bristuron OR centonuron OR centyl OR esberizid OR naturetin OR naturine OR neo naclex OR neonaclex OR naturetin OR naturine OR neonadex OR pluryl OR pluryle OR repicin OR salures OR sinesalin OR urizid) AND INREGISTER
#7 (bumetanide OR budema OR bumedyl OR bumelex OR bumet OR bumetamide OR bumethanide OR bumetidine OR bumex OR burinax OR burinex OR busix OR butinat OR butinon OR bymex OR cambiex OR drenural OR farmadiuril OR fontego OR fordiuran OR lixil OR lunetoron OR miccil) AND INREGISTER
#8 (butizide OR buthiazide OR eunephran OR eunepran OR isobutylhydrochlorothiazide OR modenol OR saltucin OR thiabulazid OR thiabutazide OR thiobulazid OR tiabutazide) AND INREGISTER
#9 (chlorothiazide OR chlorosal OR chlorothiazid OR chlorothiazidum OR chlorothiazine OR chlorthiazide OR chlotride OR diachlor OR diuril OR diurilix OR diuriwas wassermann milano OR flumen OR lyovac OR saluric OR warduzuide) AND INREGISTER
#10 (chlorthalidone OR aquadon OR chlorphthalidolone OR chlortalidon OR chlortalidone OR clortalidone OR chlorthalidine OR chlorthalidon OR chlorthialidone OR clortalil OR edemdal OR hidronal OR higroton OR higrotona OR hygroton OR hylidone OR hypertol OR hythalton OR igrolina OR igroton OR isoren OR natriuran OR oxodolin OR oxodoline OR phthalamidine OR phthalamodine OR phthalamudine OR renon OR servidone OR thalitone OR urandil OR urofinil OR zambesil) AND INREGISTER
#11 (cicletanine OR cicletanide OR cycletanide OR justar OR tenstaten OR tenstatin) AND INREGISTER
#12 (clopamide OR adurix OR aquez OR brinaldix OR brinaldrix OR brinedine OR chlosudimeprimylum clopamid OR clopamidum OR clopamine) AND INREGISTER
#13 (clorexone OR chlorexolone OR flonatril OR klorex OR nefrolan OR cyclothizaide OR anhydron OR doburil OR fluidil OR valmiran) AND INREGISTER
#14 (cyclopenthiazide OR cyclomethiazide OR cyclopenthiazine OR cyclopentiazide OR navidex OR navidrex OR navidrix OR salimid OR tsiklometiazid) AND INREGISTER
#15 (diapamide OR thiamizide OR tiamizide OR fenquizone OR idrolone) AND INREGISTER
#16 (eplerenone OR elecor OR eplerenon OR epoxymexrenone OR inspra) AND INREGISTER
#17 (ethacrynic acid OR edecril OR edecrin OR edecrina OR endecril OR etacrinic acid OR etacrynate OR etacrynic acid OR ethacrinic acid OR ethacrynate OR ethacryonic acid OR ethocrynic acid OR ethycrynic acid OR hydromedin OR lyovac sodium edecrin OR "mk 595" OR "nsc 85791" OR reomax OR sodium ethacrynate OR uregit OR uregyt) AND INREGISTER
#18 (etozolin OR elkapin OR etazolin OR etozoline OR ozolinone ethyl ester) AND INREGISTER
#19 (furosemide OR aldic OR aluzine OR anfuramaide OR aquarid OR arasemide OR cetasix OR desal OR diamazon OR dirine OR discoid OR diumide OR diural OR diuresal OR diurin OR diurix OR diurolasa OR diusemide OR diuspec OR dryptal OR durafurid OR edenol OR errolon OR eutensin OR eutensine OR flurosemide OR franyl OR fretic OR frumid OR frusedan OR frusehexal OR frusema OR frusemidor frusemide OR frusid OR fruzex OR fumarenid OR fumide OR furanthril OR furantral OR furantril OR furanturil OR furasemide OR furesin OR furesis OR furetic OR furix OR furmid OR furo puren OR furo-basan OR furo-puren OR furobasan OR furomen OR furomex OR furomide OR furomin OR furopuren OR furorese OR furosamide OR furoscan OR furose OR furosemid OR furosemix OR furosimide OR furosix OR furovite OR fursemide OR fusid OR fusimex OR hissuflux OR hydro rapid OR impugan OR jufurix OR kofuzon OR kutrix OR lasiletten OR lasilix OR lasix OR laxis OR laxur OR luramide OR marsemide OR mirfat OR odemase OR odemex OR oedemase OR oedemex OR pharmix OR promedes OR radisemide OR rasitol OR retep OR salinex OR seguril OR selectofur OR sigasalur OR uremide OR uresix OR urex-m OR vesix OR zafurida) AND INREGISTER
#20 (hydrochlorothiazide OR apo-hydro OR aquarius OR aquazide OR bisalunil OR bpzide OR bremil OR chlorosulthiadil OR chlorsulfonamidodihydrobenzothiadiazine OR cidrex OR clothia OR dehydratin OR diaqua OR dichlorosal OR dichlothiazide OR dichlotride OR dichlozid OR diclotride OR didralin OR dihydrochlORothiazide OR dihydrodiuril OR direma OR disaluril OR disothiazide OR dithiazide OR diu melusin OR diumelusin OR diurace OR diurex OR esidrex OR esidrix OR fluvin OR hctz OR hidrenox OR hidril OR hidroronol OR hidrosaluretil OR hudorex OR hychlozide OR hydrex-semi OR hydril OR hydro aquil OR hydrochlor OR hydrochloro thiazide OR hydrochlorothiamide OR hydrochlorothiazid OR hydrochlorothiazine OR hydrochlorzide OR hydrochlothiazide OR hydro diuril OR hydrodiuril OR hydromal OR hydrororonol OR hydro saluric OR hydrosaluric OR hydrothide OR hydro tonuron OR hydrozide OR hypothiazid OR hypothiazide OR ivaugan OR maschitt OR microzide OR mictrin OR nefrix OR neoflumen OR newtolide OR niagar OR oretic OR pantemon OR ridaq OR sectrazide OR tandiur OR thiadril OR thiaretic OR thiuretic OR urodiazin OR urodiazine OR urozide OR vetidrex) AND INREGISTER

#21 (hydroflumethiazide OR bristab OR di ademil OR diademil OR dihydroflumethiazide OR diraudixin OR diucardin OR hiserpin OR hydrenox OR leodrin OR leodrine OR metflorylthiadiazine OR naclex OR rontyl OR saluron OR sisuril OR trifluoromethylhydrothiazide) AND INREGISTER
#22 (indapamide OR agelan OR apadex OR arifon OR damide OR dapamax OR diflerix OR dixamid OR extur OR fludex OR fluidema OR frumeron OR indahexal OR indalix OR indamol OR indapam OR indapress OR indicontin OR indoline OR indopamide OR inpamide OR insig OR ipamix OR lorvas OR loxide OR lozol OR metindamide OR millibar OR naplin OR natrilix OR natrix OR noranat OR pamid OR pressural OR pretanix OR rinalix OR sicco OR tandix OR tertensif OR veroxil) AND INREGISTER
#23 (indacrinone OR indacrinic acid OR indacrynic acid) AND INREGISTER
#24 (mefruside OR bay caron OR baycaron OR baycarone OR mefrusid) AND INREGISTER
#25 (metolazone OR barolyn OR diulo OR metalazone OR metenix OR metolazon OR miclox OR microx OR mykrox OR normelan OR xuret OR zaroxolyn) AND INREGISTER
#26 (methylclothiazide OR aquatensen OR enduron OR enduron-m OR enduronum OR methyclothiazide OR methylchlorothiazide OR thiazidil) AND INREGISTER
#27 (muzolimine OR edrul OR musolimino) AND INREGISTER
#28 ozolinone AND INREGISTER
#29 phenoxybenzoic acid AND INREGISTER
#30 (piretanide OR arelix OR arlix OR eurelix OR lafax OR perbilen OR tauliz) AND INREGISTER
#31 (polythiazide OR drenusil OR nephril OR polythiazide OR renese) AND INREGISTER
#32 (quinethazone OR aquamox OR chinethazon OR chinethazone OR guinethazone OR hydromox OR kinetazone OR quinethazon) AND INREGISTER
#33 (spironolactone OR abbolactone OR acelat OR adultmin OR alaton OR alatone OR aldace OR aldactone OR aldopur OR aldospirone OR almatol OR aquareduct OR berlactone OR carospir OR diram OR duraspiron OR "dyta urese" OR dytaurese OR espironolactona OR flumach OR frumikal OR jenaspiron OR hypazon OR idrolattone OR merabis OR "novo spiroton" OR "novo-spiriton" OR novospiroton OR osiren OR osyrol OR pirolacton OR pondactone OR practon OR prilactone OR resacton OR spiractin OR spiridon OR spirix OR spirobeta OR "spiro ct" OR spiroctan OR spirogamma OR spirohexal OR spirolacton OR spirolactone OR spirolang OR "spiro l.u.t." OR spiron OR spirone OR spironex OR spirono isis OR spironol OR spironolacton OR spironolakton OR spironone OR spirospare OR spirothiobarbiturate OR spirotone OR spiro von ct OR supra puren OR suprapuren OR uractone OR veroshpiron OR verospiron OR verospirone OR xenalon OR youlactone) AND INREGISTER
#34 (ticrynafen OR diflurex OR selacryn OR selacryn OR thienilic acid OR thienylic acid OR tienilic acid) AND INREGISTER
#35 tizolemide AND INREGISTER
#36 (torsemide OR "bm 02015" OR "bm 2015" OR bm02015 OR bm2015 OR demadex OR diuremid OR "jdl 464" OR jdl464 OR luprac OR presaril OR toradiur OR torem OR torrem OR torasemide OR unat OR upcard) AND INREGISTER
#37 (triamterene OR dyrenium OR dytac OR urocaudal OR ademin OR ademine OR dyren OR dyrenium OR dytac OR iatropur OR jatropur OR noridyl OR pterofen OR pterophene OR teriam OR triampterene OR triamterence OR triamterens OR triamteril OR triteren OR uretren OR urocaudal) AND INREGISTER
#38 (trichloromethiazide OR aquazide OR dichloromethylhydrochlorothiazide OR diurese OR esmarin OR eurinol OR fluitran OR flutra OR gangesol OR hydrotrichlorothiazide OR metahydrin OR methahydrin OR naqua OR naquasone OR salurin OR triazide OR trichlordiuride OR trichlorex OR trichlormethazide OR trichlormethiazide OR trichlormas OR trichloromethylhydrochlorothiazide OR triflumen OR wadel) AND INREGISTER
#39 (tripamide OR normonal) AND INREGISTER
#40 (xipamide OR aquaforil OR aquaphor OR aquaphoril OR aquavor OR diurexan OR lumitens OR xipamid OR xypamide OR zipix) AND INREGISTER
#41 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)
#42 angiotensin converting enzyme inhibit* AND INREGISTER
#43 ace NEAR2 inhibit* AND INREGISTER
#44 acei OR aceis AND INREGISTER
#45 (alacepril OR altiopril OR ancovenin OR benazepril OR captopril OR ceranapril OR ceronapril OR cilazapril OR deacetylalacepril OR delapril OR derapril OR enalapril OR epicaptopril OR fasidotril OR fosinopril OR foroxymithine OR gemopatrilat OR idapril OR imidapril OR indolapril OR libenzapril OR lisinopril OR moexipril OR moveltipril OR omapatrilat OR pentopril* OR perindopril* OR pivopril OR quinapril* OR ramipril* OR rentiapril OR saralasin OR s nitrosocaptopril OR spirapril* OR temocapril* OR teprotide OR trandolapril* OR utibapril* OR zabicipril* OR zofenopril*) AND INREGISTER
#46 (#42 OR #43 OR #44 OR #45)
#47 ((angiotensin receptor antagonist*) OR (angiotensin receptor block*)) AND INREGISTER
#48 (arb OR arbs) AND INREGISTER
#49 (abitesartan OR azilsartan OR candesartan OR elisartan OR embusartan OR eprosartan OR forasartan OR irbesartan OR losartan OR milfasartan OR olmesartan OR saprisartan OR tasosartan OR telmisartan OR valsartan OR zolasartan) AND INREGISTER
#50 (#47 OR #48 OR #49)
#51 ((calcium channel antagon*) OR (calcium channel block*) OR (calcium inhibit*)) AND INREGISTER
#52 (amlodipine OR amrinone OR aranidipine OR barnidipine OR bencyclane OR benidipine OR bepridil OR cilnidipine OR cinnarizine OR clentiazem OR darodipine OR diltiazem OR efonidipine OR elgodipine OR etafenone OR fantofarone OR felodipine OR fendiline OR

flunarizine OR gallopamil OR isradipine OR lacidipine OR lercanidipine OR lidoflazine OR lomerizine OR manidipine OR mibefradil OR nicardipine OR nifedipine OR niguldipine OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR perhexiline OR prenylamine OR semotiadil OR terodiline OR tiapamil OR verapamil) AND INREGISTER
#53 (#51 OR #52)
#54 (methyldopa OR alphamethyldopa OR amodopa OR dopamet OR dopegyt OR dopegit OR dopegite OR emdopa OR hyperpax OR hyperpaxa OR methylpropionic acid OR dopergit OR meldopa OR methyldopate OR medopa OR medomet OR sembrina OR aldomet OR aldometil OR aldomin OR hydopa OR methyldihydroxyphenylalanine OR methyl dopa OR mulfasin OR presinol OR presolisin OR sedometil OR sembrina OR taquinil OR dihydroxyphenylalanine OR methylphenylalanine OR methylalanine OR alpha methyl dopa) AND INREGISTER
#55 (reserpine OR serpentina OR rauwolfia OR serpasil) AND INREGISTER
#56 (clonidine OR adesipress OR arkamin OR caprysin OR catapres* OR catasan OR chlofazolin OR chlophazolin OR clinidine OR clofelin* OR clofenil OR clomidine OR clondine OR clonistada OR clonnirit OR clophelin* OR dichlorophenylaminoimidazoline OR dixarit OR duraclon OR gemiton OR haemiton OR hemiton OR imidazoline OR isoglaucon OR klofelin OR klofenil OR normopresan OR paracefan OR tesno timelets) AND INREGISTER
#57 (hydralazin* OR hydrallazin* OR hydralizine OR hydrazinophtalazine OR hydrazinophthalazine OR hydrazinophtalizine OR dralzine OR hydralacin OR hydrolazine OR hypophthalin OR hypoftalin OR hydrazinophthalazine OR idralazina OR 1-hydrazinophthalazine OR apressin OR nepresol OR apressoline OR apresoline OR apresolin OR alphapress OR alazine OR idralazina OR lopress OR plethorit OR praeparat) AND INREGISTER
#58 (#54 OR #55 OR #56 OR #57)
#59 ((adrenergic beta-antagon*) OR (beta adrenergic*) OR (beta antagon*) OR (beta block*) OR (beta recept*)) AND INREGISTER
#60 (acebutolol OR adimolol OR afurolol OR alprenolol OR amosulalol OR arotinolol OR atenolol OR befunolol OR betaxolol OR bevantolol OR bisoprolol OR bopindolol OR bornaprolol OR brefonalol OR bucindolol OR bucumolol OR bufetolol OR bufuralol OR bunitrolol OR bunolol OR bupranolol OR butofilolol OR butoxamine OR carazolol OR carteolol OR carvedilol OR celiprolol OR cetamolol OR chlORtalidone clORanolol OR cyanoiodopindolol OR cyanopindolol OR deacetylmetipranolol OR diacetolol OR dihydroalprenolol OR dilevalol OR epanolol OR esmolol OR exaprolol OR falintolol OR flestolol OR flusoxolol OR hydroxybenzylpinodolol OR hydroxycarteolol OR hydroxymetoprolol OR indenolol OR iodocyanopindolol OR iodopindolol OR iprocrolol OR isoxaprolol OR labetalol OR landiolol OR levobunolol OR levomoprolol OR medroxalol OR mepindolol OR methylthiopropranolol OR metipranolol OR metoprolol OR moprolol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR nadolol OR nebivolol OR nifenalol OR nipradilol OR oxprenolol OR pafenolol OR pamatolol OR penbutolol OR pindolol OR practolol OR primidolol OR prizidilol OR procinolol OR pronetalol OR propranolol OR proxodolol OR ridazolol OR salcardolol OR soquinolol OR sotalol OR spirendolol OR talinolol OR tertatolol OR tienoxolol OR tilisolol OR timolol OR tolamolol OR toliprolol OR tribendilol OR xibenolol) AND INREGISTER
#61 (#59 OR #60)
#62 ((adrenergic alpha) OR (adrenergic antagon*) OR (adrenergic block*) OR (adrenergic receptor antagon*) OR (adrenergic receptor block*) OR (alpha block*)) AND INREGISTER
#63 (alfuzosin OR bunazosin OR doxazosin OR metazosin OR neldazosin OR prazosin OR silodosin OR tamsulosin OR terazosin OR tiodazosin OR trimazosin) AND INREGISTER
#64 (#62 OR #63)
#65 (#46 OR #50 OR #53 OR #58 OR #61 OR #64)
#66 RCT:DE AND INREGISTER
#67 Review:ODE AND INREGISTER
#68 (#66 OR #67)
#69 (#41 AND #65 AND #68)

Database: Cochrane Central Register of Controlled Trials (Issue 2, 2021) via Cochrane Register of Studies

Search Date: 25 March 2021

#1 thiazide* AND CENTRAL:TARGET
#2 sodium chloride NEAR2 (cotransporter inhibit* OR co-transporter inhibit* OR symporter inhibit*) AND CENTRAL:TARGET
#3 (ceiling OR loop OR potassium-depleting) NEAR2 diuretic* AND CENTRAL:TARGET
#4 (amiloride OR amiclaran OR amidal OR amiduret trom OR amikal OR "amilo 5" OR amiloberag OR amilorid OR amiloridehydrochlorhydrate OR amiloridine OR amipramidine OR amyloride OR arumil OR berkamil OR colectril OR guanamprazine OR kaluril OR medamor OR midamor OR midoride OR "mk 870" OR modamide OR nirulid OR pandiuren) AND CENTRAL:TARGET
#5 (azosemide OR azosemid OR luret OR "ple 1053" OR "sk 110") AND CENTRAL:TARGET
#6 (bendroflumethiazide OR aprinox OR bendrofluazide OR bendroflumethiazide OR benzhydroflumethiazide OR benzydroflumethiazide OR benzyl hydroflumethiazide OR benzylhydroflumethiazide OR benzide OR berkozide OR bristuron OR centonuron OR centyl OR esberizid OR naturetin OR naturine OR neo naclex OR neonaclex OR naturetin OR naturine OR neonadex OR pluryl OR pluryle OR repicin OR salures OR sinesalin OR urizid) AND CENTRAL:TARGET
#7 (bumetanide OR budema OR bumedyl OR bumelex OR bumet OR bumetamide OR bumethanide OR bumetidine OR bumex OR burinax OR burinex OR busix OR butinat OR butinon OR bymex OR cambiex OR drenural OR farmadiuril OR fontego OR fordiuran OR lixil OR

lunetoron OR miccil OR "pf 1593" OR "pf-1593" OR pf1593 OR primex OR "ro 10 6338" OR "ro 10-6338" OR "ro10 6338" OR ro10-6338) AND CENTRAL:TARGET
#8 (butizide OR buthiazide OR eunephran OR eunepran OR isobutylhydrochlorothiazide OR modenol OR saltucin OR thiabulazid OR thiabutazide OR thiobulazid OR tiabutazide) AND CENTRAL:TARGET
#9 (chlorothiazide OR chlorosal OR chlorothiazid OR chlorothiazidum OR chlorothiazine OR chlorthiazide OR chlotride OR diachlor OR diuril OR diurilix OR diuriwas wassermann milano OR flumen OR lyovac OR saluric OR warduzuide) AND CENTRAL:TARGET
#10 (chlorthalidone OR aquadon OR chlorphthalidolone OR chlortalidon OR chlortalidone OR clortalidone OR chlorthalidine OR chlorthalidon OR chlorthialidone OR clortalil OR edemdal OR hidronal OR higroton OR higrotona OR hygroton OR hylidone OR hypertol OR hythalton OR igrolina OR igroton OR isoren OR natriuran OR oxodolin OR oxodoline OR phthalamidine OR phthalamodine OR phthalamudine OR renon OR servidone OR thalitone OR urandil OR urofinil OR zambesil) AND CENTRAL:TARGET
#11 (cicletanine OR "bn 1270" OR "bn 50417" OR "bn 50418" OR bn1270 OR bn50417 OR bn50418 OR cicletanide OR cycletanide OR justar OR tenstaten OR tenstatin) AND CENTRAL:TARGET
#12 (clopamide OR adurix OR aquez OR brinaldix OR brinaldrix OR brinedine OR chlosudimeprimylum clopamid OR clopamidum OR clopamine) AND CENTRAL:TARGET
#13 (clorexone OR chlorexolone OR flonatril OR klorex OR nefrolan OR cyclothizaide OR anhydron OR doburil OR fluidil OR valmiran) AND CENTRAL:TARGET
#14 (cyclopenthiazide OR cyclomethiazide OR cyclopenthiazine OR cyclopentiazide OR navidex OR navidrex OR navidrix OR salimid OR tsiklometiazid) AND CENTRAL:TARGET
#15 (diapamide OR thiamizide OR tiamizide OR fenquizone OR idrolone) AND CENTRAL:TARGET
#16 (eplerenone OR "cgp 30 083" OR "cgp 30083" OR cgp30083 OR elecor OR eplerenon OR epoxymexrenone OR inspra OR "sc 66110" OR sc66110) AND CENTRAL:TARGET
#17 (ethacrynic acid OR edecril OR edecrin OR edecrina OR endecril OR etacrinic acid OR etacrynate OR etacrynic acid OR ethacrinic acid OR ethacrynate OR ethacryonic acid OR ethocrynic acid OR ethycrynic acid OR hydromedin OR lyovac sodium edecrin OR "mk 595" OR "nsc 85791" OR reomax OR sodium ethacrynate OR uregit OR uregyt) AND CENTRAL:TARGET
#18 (etozolin OR elkapin OR etazolin OR etozoline OR "go 687" OR go687 OR "goe 687" OR goe687 OR ozolinone ethyl ester OR "w 2900" OR w2900) AND CENTRAL:TARGET
#19 (furosemide OR aldic OR aluzine OR anfuramaide OR aquarid OR arasemide OR cetasix OR desal OR diamazon OR dirine OR discoid OR diumide OR diural OR diuresal OR diurin OR diurix OR diurolasa OR diusemide OR diuspec OR dryptal OR durafurid OR edenol OR errolon OR eutensin OR eutensine OR flurosemide OR franyl OR fretic OR frumid OR frusedan OR frusehexal OR frusema OR frusemidor frusemide OR frusid OR fruzex OR fumarenid OR fumide OR furanthril OR furantral OR furantril OR furanturil OR furasemide OR furesin OR furesis OR furetic OR furix OR furmid OR furo puren OR furo-basan OR furo-puren OR furobasan OR furomen OR furomex OR furomide OR furomin OR furopuren OR furorese OR furosamide OR furoscan OR furose OR furosemid OR furosemix OR furosimide OR furosix OR furovite OR fursemide OR fusid OR fusimex OR hissuflux OR hydro rapid OR impugan OR jufurix OR kofuzon OR kutrix OR lasiletten OR lasilix OR lasix OR laxis OR laxur OR "lb 502" OR lb502 OR luramide OR marsemide OR mirfat OR odemase OR odemex OR oedemase OR oedemex OR pharmix OR promedes OR radisemide OR rasitol OR retep OR salinex OR seguril OR selectofur OR sigasalur OR uremide OR uresix OR urex-m OR vesix OR zafurida) AND CENTRAL:TARGET
#20 (hydrochlorothiazide OR apo-hydro OR aquarius OR aquazide OR bisalunil OR bpzide OR bremil OR chlorosulthiadil OR chlorsulfonamidodihydrobenzothiadiazine OR cidrex OR clothia OR dehydratin OR diaqua OR dichlorosal OR dichlothiazide OR dichlotride OR dichlozid OR diclotride OR didralin OR dihydrochlORothiazide OR dihydrodiuril OR direma OR disaluril OR disothiazide OR dithiazide OR diu melusin OR diumelusin OR diurace OR diurex OR esidrex OR esidrix OR fluvin OR hctz OR hidrenox OR hidril OR hidroronol OR hidrosaluretil OR hudorex OR hychlozide OR hydrex-semi OR hydril OR hydro aquil OR hydrochlor OR hydrochloro thiazide OR hydrochlorothiamide OR hydrochlorothiazid OR hydrochlorothiazine OR hydrochlorzide OR hydrochlothiazide OR hydro diuril OR hydrodiuril OR hydromal OR hydrororonol OR hydro saluric OR hydrosaluric OR hydrothide OR hydro tonuron OR hydrozide OR hypothiazid OR hypothiazide OR ivaugan OR maschitt OR microzide OR mictrin OR nefrix OR neoflumen OR newtolide OR niagar OR oretic OR pantemon OR ridaq OR sectrazide OR tandiur OR thiadril OR thiaretic OR thiuretic OR urodiazin OR urodiazine OR urozide OR vetidrex) AND CENTRAL:TARGET
#21 (hydroflumethiazide OR bristab OR di ademil OR diademil OR dihydroflumethiazide OR diraudixin OR diucardin OR hiserpin OR hydrenox OR leodrin OR leodrine OR metflorylthiadiazine OR naclex OR rontyl OR saluron OR sisuril OR trifluoromethylhydrothiazide) AND CENTRAL:TARGET
#22 (indapamide OR agelan OR apadex OR arifon OR damide OR dapamax OR diflerix OR dixamid OR extur OR fludex OR fluidema OR frumeron OR indahexal OR indalix OR indamol OR indapam OR indapress OR indicontin OR indoline OR indopamide OR inpamide OR insig OR ipamix OR lorvas OR loxide OR lozol OR metindamide OR millibar OR naplin OR natrilix OR natrix OR noranat OR pamid OR pressural OR pretanix OR rinalix OR sicco OR tandix OR tertensif OR veroxil) AND CENTRAL:TARGET
#23 (indacrinone OR indacrinic acid OR indacrynic acid OR "mk 196") AND CENTRAL:TARGET
#24 (mefruside OR bay caron OR bay1500 OR baycaron OR baycarone OR mefrusid) AND CENTRAL:TARGET
#25 (metolazone OR barolyn OR diulo OR metalazone OR metenix OR metolazon OR miclox OR microx OR mykrox OR normelan OR xuret OR zaroxolyn) AND CENTRAL:TARGET
#26 (methylclothiazide OR aquatensen OR enduron OR enduron-m OR enduronum OR methyclothiazide OR methylchlorothiazide OR thiazidil) AND CENTRAL:TARGET
#27 (muzolimine OR "bay g 2821" OR "bay g2821" OR "bayer g 2821" OR "bayer g2821" OR edrul OR musolimino) AND CENTRAL:TARGET
#28 (ozolinone OR "go 3282" OR go3282 OR "goe 3282" OR goe3282 OR "goedecke 3282") AND CENTRAL:TARGET
#29 phenoxybenzoic acid AND CENTRAL:TARGET

#30 (piretanide OR arelix OR arlix OR eurelix OR "hoe 118" OR hoe118 OR lafax OR perbilen OR "s 73 4118" OR "s 734118" OR s734118 OR tauliz) AND CENTRAL:TARGET
#31 (polythiazide OR drenusil OR nephril OR polythiazide OR renese) AND CENTRAL:TARGET
#32 (quinethazone OR aquamox OR chinethazon OR chinethazone OR guinethazone OR hydromox OR kinetazone OR quinethazon) AND CENTRAL:TARGET
#33 (spironolactone OR abbolactone OR acelat OR adultmin OR alaton OR alatone OR aldace OR aldactone OR aldopur OR aldospirone OR almatol OR aquareduct OR berlactone OR carospir OR "crl 635" OR crl635 OR diram OR duraspiron OR "dyta urese" OR dytaurese OR espironolactona OR flumach OR frumikal OR jenaspiron OR hypazon OR idrolattone OR merabis OR "novo spiroton" OR "novo-spiriton" OR novospiroton OR osiren OR osyrol OR pirolacton OR pondactone OR practon OR prilactone OR resacton OR "sas 1060" OR sas1060 OR "sc 9420" OR "sc-9420" OR sc9420 OR spiractin OR spiridon OR spirix OR spirobeta OR "spiro ct" OR spiroctan OR spirogamma OR spirohexal OR spirolacton OR spirolactone OR spirolang OR "spiro l.u.t." OR spiron OR spirone OR spironex OR spirono isis OR spironol OR spironolacton OR spironolakton OR spirononе OR spirospare OR spirothiobarbiturate OR spirotone OR spiro von ct OR supra puren OR suprapuren OR uractone OR veroshpiron OR verospiron OR verospirone OR xenalon OR youlactone) AND CENTRAL:TARGET
#34 (ticrynafen OR "anp 3624" OR "anp-3624" OR anp3624 OR diflurex OR selacryn OR "skf 62698" OR "skf-62698" OR skf62698 OR selacryn OR thienilic acid OR thienylic acid OR tienilic acid) AND CENTRAL:TARGET
#35 tizolemide AND CENTRAL:TARGET
#36 (torsemide OR "bm 02015" OR "bm 2015" OR bm02015 OR bm2015 OR demadex OR diuremid OR "jdl 464" OR jdl464 OR luprac OR presaril OR toradiur OR torem OR torrem OR torasemide OR unat OR upcard) AND CENTRAL:TARGET
#37 (triamterene OR dyrenium OR dytac OR urocaudal OR ademin OR ademine OR dyren OR dyrenium OR dytac OR iatropur OR jatropur OR noridyl OR "nsc 77625" OR nsc77625 OR pterofen OR pterophene OR "sk and f 8542" OR "skf 8542" OR skf8542 OR teriam OR triampterene OR triamterence OR triamterens OR triamteril OR triteren OR uretren OR urocaudal) AND CENTRAL:TARGET
#38 (trichloromethiazide OR aquazide OR dichloromethylhydrochlorothiazide OR diurese OR esmarin OR eurinol OR fluitran OR flutra OR gangesol OR hydrotrichlorothiazide OR metahydrin OR methahydrin OR naqua OR naquasone OR salurin OR triazide OR trichlordiuride OR trichlorex OR trichlormethazide OR trichlormethiazide OR trichlormas OR trichloromethylhydrochlorothiazide OR triflumen OR wadel) AND CENTRAL:TARGET
#39 (tripamide OR "adr 033" OR adr033 OR "e 614" OR e614 OR normonal) AND CENTRAL:TARGET
#40 (xipamide OR aquaforil OR aquaphor OR aquaphoril OR aquavor OR "bei 1293" OR diurexan OR lumitens OR xipamid OR xypamide OR zipix) AND CENTRAL:TARGET
#41 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40) AND CENTRAL:TARGET
#42 angiotensin converting enzyme inhibit* AND CENTRAL:TARGET
#43 ace NEAR2 inhibit* AND CENTRAL:TARGET
#44 acei OR aceis AND CENTRAL:TARGET
#45 (alacepril OR altiopril OR ancovenin OR benazepril OR captopril OR ceranapril OR ceronapril OR cilazapril OR deacetylalacepril OR delapril OR derapril OR enalapril OR epicaptopril OR fasidotril OR fosinopril OR foroxymithine OR gemopatrilat OR idapril OR imidapril OR indolapril OR libenzapril OR lisinopril OR moexipril OR moveltipril OR omapatrilat OR pentopril* OR perindopril* OR pivopril OR quinapril* OR ramipril* OR rentiapril OR saralasin OR s nitrosocaptopril OR spirapril* OR temocapril* OR teprotide OR trandolapril* OR utibapril* OR zabicipril* OR zofenopril*) AND CENTRAL:TARGET
#46 (#42 OR #43 OR #44 OR #45) AND CENTRAL:TARGET
#47 ((angiotensin receptor antagonist*) OR (angiotensin receptor block*)) AND CENTRAL:TARGET
#48 (arb OR arbs) AND CENTRAL:TARGET
#49 (abitesartan OR azilsartan OR candesartan OR elisartan OR embusartan OR eprosartan OR forasartan OR irbesartan OR losartan OR milfasartan OR olmesartan OR saprisartan OR tasosartan OR telmisartan OR valsartan OR zolasartan) AND CENTRAL:TARGET
#50 (#47 OR #48 OR #49) AND CENTRAL:TARGET
#51 ((calcium channel antagon*) OR (calcium channel block*) OR (calcium inhibit*)) AND CENTRAL:TARGET
#52 (amlodipine OR amrinone OR aranidipine OR barnidipine OR bencyclane OR benidipine OR bepridil OR cilnidipine OR cinnarizine OR clentiazem OR darodipine OR diltiazem OR efonidipine OR elgodipine OR etafenone OR fantofarone OR felodipine OR fendiline OR flunarizine OR gallopamil OR isradipine OR lacidipine OR lercanidipine OR lidoflazine OR lomerizine OR manidipine OR mibefradil OR nicardipine OR nifedipine OR niguldipine OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR perhexiline OR prenylamine OR semotiadil OR terodiline OR tiapamil OR verapamil) AND CENTRAL:TARGET
#53 (#51 OR #52) AND CENTRAL:TARGET
#54 (methyldopa OR alphamethyldopa OR amodopa OR dopamet OR dopegyt OR dopegit OR dopegite OR emdopa OR hyperpax OR hyperpaxa OR methylpropionic acid OR dopergit OR meldopa OR methyldopate OR medopa OR medomet OR sembrina OR aldomet OR aldometil OR aldomin OR hydopa OR methyldihydroxyphenylalanine OR methyl dopa OR mulfasin OR presinol OR presolisin OR sedometil OR sembrina OR taquinil OR dihydroxyphenylalanine OR methylphenylalanine OR methylalanine OR alpha methyl dopa) AND CENTRAL:TARGET
#55 (reserpine OR serpentina OR rauwolfia OR serpasil) AND CENTRAL:TARGET
#56 (clonidine OR adesipress OR arkamin OR caprysin OR catapres* OR catasan OR chlofazolin OR chlophazolin OR clinidine OR clofelin* OR clofenil OR clomidine OR clondine OR clonistada OR clonnirit OR clophelin* OR dichlorophenylaminoimidazoline OR dixarit OR duraclon OR gemiton OR haemiton OR hemiton OR imidazoline OR isoglaucon OR klofelin OR klofenil OR normopresan OR paracefan OR tesno timelets) AND CENTRAL:TARGET

#57 (hydralazin* OR hydrallazin* OR hydralizine OR hydrazinophtalazine OR hydrazinophthalazine OR hydrazinophtalizine OR dralzine OR hydralacin OR hydrolazine OR hypophthalin OR hypoftalin OR hydrazinophthalazine OR idralazina OR 1-hydrazinophthalazine OR apressin OR nepresol OR apressoline OR apresoline OR apresolin OR alphapress OR alazine OR idralazina OR lopress OR plethorit OR praeparat) AND CENTRAL:TARGET
#58 (#54 OR #55 OR #56 OR #57) AND CENTRAL:TARGET
#59 ((adrenergic beta-antagon*) OR (beta adrenergic*) OR (beta antagon*) OR (beta block*) OR (beta recept*)) AND CENTRAL:TARGET
#60 (acebutolol OR adimolol OR afurolol OR alprenolol OR amosulalol OR arotinolol OR atenolol OR befunolol OR betaxolol OR bevantolol OR bisoprolol OR bopindolol OR bornaprolol OR brefonalol OR bucindolol OR bucumolol OR bufetolol OR bufuralol OR bunitrolol OR bunolol OR bupranolol OR butofilolol OR butoxamine OR carazolol OR carteolol OR carvedilol OR celiprolol OR cetamolol OR chlORtalidone clORanolol OR cyanoiodopindolol OR cyanopindolol OR deacetylmetipranolol OR diacetolol OR dihydroalprenolol OR dilevalol OR epanolol OR esmolol OR exaprolol OR falintolol OR flestolol OR flusoxolol OR hydroxybenzylpinodolol OR hydroxycarteolol OR hydroxymetoprolol OR indenolol OR iodocyanopindolol OR iodopindolol OR iprocrolol OR isoxaprolol OR labetalol OR landiolol OR levobunolol OR levomoprolol OR medroxalol OR mepindolol OR methylthiopropranolol OR metipranolol OR metoprolol OR moprolol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR nadolol OR nebivolol OR nifenalol OR nipradilol OR oxprenolol OR pafenolol OR pamatolol OR penbutolol OR pindolol OR practolol OR primidolol OR prizidilol OR procinolol OR pronetalol OR propranolol OR proxodolol OR ridazolol OR salcardolol OR soquinolol OR sotalol OR spirendolol OR talinolol OR tertatolol OR tienoxolol OR tilisolol OR timolol OR tolamolol OR toliprolol OR tribendilol OR xibenolol) AND CENTRAL:TARGET
#61 (#59 OR #60) AND CENTRAL:TARGET
#62 ((adrenergic alpha) OR (adrenergic antagon*) OR (adrenergic block*) OR (adrenergic receptor antagon*) OR (adrenergic receptor block*) OR (alpha block*)) AND CENTRAL:TARGET
#63 (alfuzosin OR bunazosin OR doxazosin OR metazosin OR neldazosin OR prazosin OR silodosin OR tamsulosin OR terazosin OR tiodazosin OR trimazosin) AND CENTRAL:TARGET
#64 (#62 OR #63) AND CENTRAL:TARGET
#65 (#46 OR #50 OR #53 OR #58 OR #61 OR #64) AND CENTRAL:TARGET
#66 MESH DESCRIPTOR Hypertension AND CENTRAL:TARGET
#67 MESH DESCRIPTOR Essential Hypertension AND CENTRAL:TARGET
#68 (antihypertens* OR hypertens*):TI,AB AND CENTRAL:TARGET
#69 (elevat* OR high OR rais*) NEAR2 blood pressur* AND CENTRAL:TARGET
#70 (#66 OR #67 OR #68 OR #69) AND CENTRAL:TARGET
#71 #41 AND #65 AND #70 AND CENTRAL:TARGET

Database: Embase <1974 to 2021 March 24>
Search Date: 25 March 2021
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1 exp thiazide diuretic agent/
2 exp loop diuretic agent/
3 thiazide*.tw.
4 ((sodium chloride adj2 cotransporter inhibit*) or (sodium chloride adj2 co-transporter inhibit*) or (sodium chloride adj2 symporter inhibit*)).tw.
5 ((ceiling adj2 diuretic*) or (loop adj2 diuretic*) or (potassium-depleting adj2 diuretic*)).tw.
6 (amiloride or amiclaran or amidal or amiduret trom or amikal or "amilo 5" or amiloberag or amilorid or amiloridehydrochlorhydrate or amiloridine or amipramidine or amyloride or arumil or berkamil or colectril or guanamprazine or kaluril or medamor or midamor or midoride or "mk 870" or modamide or nirulid or pandiuren).mp.
7 (azosemide or azosemid or luret or "ple 1053" or "sk 110").mp.
8 (bendroflumethiazide or aprinox or bendrofluazide or bendroflumethiazide or benzhydroflumethiazide or benzydroflumethiazide or benzyl hydroflumethiazide or benzylhydroflumethiazide or benzide or berkozide or bristuron or centonuron or centyl or esberizid or naturetin or naturine or neo naclex or neonaclex or naturetin or naturine or neonadex or pluryl or pluryle or repicin or salures or sinesalin or urizid).mp.
9 (bumetanide or budema or bumedyl or bumelex or bumet or bumetamide or bumethanide or bumetidine or bumex or burinax or burinex or busix or butinat or butinon or bymex or cambiex or drenural or farmadiuril or fontego or fordiuran or lixil or lunetoron or miccil or "pf 1593" or "pf-1593" or pf1593 or primex or "ro 10 6338" or "ro 10-6338" or "ro10 6338" or ro10-6338).mp.
10 (butizide or buthiazide or eunephran or eunepran or isobutylhydrochlorothiazide or modenol or saltucin or thiabulazid or thiabutazide or thiobulazid or tiabutazide).mp.
11 (chlorothiazide or chlorosal or chlorothiazid or chlorothiazidum or chlorothiazine or chlorthiazide or chlotride or diachlor or diuril or diurilix or diuriwas wassermann milano or flumen or lyovac or saluric or warduzuide).mp.
12 (chlorthalidone or aquadon or chlorphthalidolone or chlortalidon or chlortalidone or clortalidone or chlorthalidine or chlorthalidon or chlorthialidone or clortalil or edemdal or hidronal or higroton or higrotona or hygroton or hylidone or hypertol or hythalton or igrolina or igroton or isoren or natriuran or oxodolin or oxodoline or phthalamidine or phthalamodine or phthalamudine or renon or servidone or thalitone or urandil or urofinil or zambesil).mp.

13 (cicletanine or "bn 1270" or "bn 50417" or "bn 50418" or bn1270 or bn50417 or bn50418 or cicletanide or cycletanide or justar or tenstaten or tenstatin).mp.
14 (clopamide or adurix or aquez or brinaldix or brinaldrix or brinedine or chlosudimeprimylum clopamid or clopamidum or clopamine).mp.
15 (clorexone or chlorexolone or flonatril or klorex or nefrolan or cyclothizaide or anhydron or doburil or fluidil or valmiran).mp.
16 (cyclopenthiazide or cyclomethiazide or cyclopenthiazine or cyclopentiazide or navidex or navidrex or navidrix or salimid or tsiklometiazid).mp.
17 (diapamide or thiamizide or tiamizide or fenquizone or idrolone).mp.
18 (eplerenone or "cgp 30 083" or "cgp 30083" or cgp30083 or elecor or eplerenon or epoxymexrenone or inspra or "sc 66110" or sc66110).mp.
19 (ethacrynic acid or edecril or edecrin or edecrina or endecril or etacrinic acid or etacrynate or etacrynic acid or ethacrinic acid or ethacrynate or ethacryonic acid or ethocrynic acid or ethycrynic acid or hydromedin or lyovac sodium edecrin or "mk 595" or "nsc 85791" or reomax or sodium ethacrynate or uregit or uregyt).mp.
20 (etozolin or elkapin or etazolin or etozoline or "go 687" or go687 or "goe 687" or goe687 or ozolinone ethyl ester or "w 2900" or w2900).mp.
21 (furosemide or aldic or aluzine or anfuramaide or aquarid or arasemide or cetasix or desal or diamazon or dirine or discoid or diumide or diural or diuresal or diurin or diurix or diurolasa or diusemide or diuspec or dryptal or durafurid or edenol or errolon or eutensin or eutensine or flurosemide or franyl or fretic or frumid or frusedan or frusehexal or frusema or frusemidor frusemide or frusid or fruzex or fumarenid or fumide or furanthril or furantral or furantril or furanturil or furasemide or furesin or furesis or furetic or furix or furmid or furo puren or furo-basan or furo-puren or furobasan or furomen or furomex or furomide or furomin or furopuren or furorese or furosamide or furoscan or furose or furosemid or furosemix or furosimide or furosix or furovite or fursemide or fusid or fusimex or hissuflux or hydro rapid or impugan or jufurix or kofuzon or kutrix or lasiletten or lasilix or lasix or laxis or laxur or "lb 502" or lb502 or luramide or marsemide or mirfat or odemase or odemex or oedemase or oedemex or pharmix or promedes or radisemide or rasitol or retep or salinex or seguril or selectofur or sigasalur or uremide or uresix or urex-m or vesix or zafurida).mp.
22 (hydrochlorothiazide or apo-hydro or aquarius or aquazide or bisalunil or bpzide or bremil or chlorosulthiadil or chlorsulfonamidodihydrobenzothiadiazine or cidrex or clothia or dehydratin or diaqua or dichlorosal or dichlothiazide or dichlotride or dichlozid or diclotride or didralin or dihydrochlorothiazide or dihydrodiuril or direma or disaluril or disothiazide or dithiazide or diu melusin or diumelusin or diurace or diurex or esidrex or esidrix or fluvin or hctz or hidrenox or hidril or hidroronol or hidrosaluretil or hudorex or hychlozide or hydrex-semi or hydril or hydro aquil or hydrochlor or hydrochloro thiazide or hydrochlorothiamide or hydrochlorothiazid or hydrochlorothiazine or hydrochlorzide or hydrochlothiazide or hydro diuril or hydrodiuril or hydromal or hydrororonol or hydro saluric or hydrosaluric or hydrothide or hydro tonuron or hydrozide or hypothiazid or hypothiazide or ivaugan or maschitt or microzide or mictrin or nefrix or neoflumen or newtolide or niagar or oretic or pantemon or ridaq or sectrazide or tandiur or thiadril or thiaretic or thiuretic or urodiazin or urodiazine or urozide or vetidrex).mp.
23 (hydroflumethiazide or bristab or di ademil or diademil or dihydroflumethiazide or diraudixin or diucardin or hiserpin or hydrenox or leodrin or leodrine or metflorylthiadiazine or naclex or rontyl or saluron or sisuril or trifluoromethylhydrothiazide).mp.
24 (indapamide or agelan or apadex or arifon or damide or dapamax or diflerix or dixamid or extur or fludex or fluidema or frumeron or indahexal or indalix or indamol or indapam or indapress or indicontin or indoline or indopamide or inpamide or insig or ipamix or lorvas or loxide or lozol or metindamide or millibar or naplin or natrilix or natrix or noranat or pamid or pressural or pretanix or rinalix or sicco or tandix or tertensif or veroxil).mp.
25 (indacrinone or indacrinic acid or indacrynic acid or "mk 196").mp.
26 (mefruside or bay caron or bay1500 or baycaron or baycarone or mefrusid).mp.
27 (metolazone or barolyn or diulo or metalazone or metenix or metolazon or miclox or microx or mykrox or normelan or xuret or zaroxolyn).mp.
28 (methylclothiazide or aquatensen or enduron or enduron-m or enduronum or methyclothiazide or methylchlorothiazide or thiazidil).mp.
29 (muzolimine or "bay g 2821" or "bay g2821" or "bayer g 2821" or "bayer g2821" or edrul or musolimino).mp.
30 (ozolinone or "go 3282" or go3282 or "goe 3282" or goe3282 or "goedecke 3282").mp.
31 phenoxybenzoic acid.mp.
32 (piretanide or arelix or arlix or eurelix or "hoe 118" or hoe118 or lafax or perbilen or "s 73 4118" or "s 734118" or s734118 or tauliz).mp.
33 (polythiazide or drenusil or nephril or polythiazide or renese).mp.
34 (quinethazone or aquamox or chinethazon or chinethazone or guinethazone or hydromox or kinetazone or quinethazon).mp.
35 (spironolactone or abbolactone or acelat or adultmin or alaton or alatone or aldace or aldactone or aldopur or aldospirone or almatol or aquareduct or berlactone or carospir or "crl 635" or crl635 or diram or duraspiron or "dyta urese" or dytaurese or espironolactona or flumach or frumikal or jenaspiron or hypazon or idrolattone or merabis or "novo spiroton" or "novo-spiriton" or novospiroton or osiren or osyrol or pirolacton or pondactone or practon or prilactone or resacton or "sas 1060" or sas1060 or "sc 9420" or "sc-9420" or sc9420 or spiractin or spiridon or spirix or spirobeta or "spiro ct" or spiroctan or spirogamma or spirohexal or spirolacton or spirolactone or spirolang or "spiro l.u.t." or spiron or spirone or spironex or spirono isis or spironol or spironolacton or spironolakton or spironone or spirospare or spirothiobarbiturate or spirotone or spiro von ct or supra puren or suprapuren or uractone or veroshpiron or verospiron or verospirone or xenalon or youlactone).mp.
36 (ticrynafen or "anp 3624" or "anp-3624" or anp3624 or diflurex or selacryn or "skf 62698" or "skf-62698" or skf62698 or selacryn or thienilic acid or thienylic acid or tienilic acid).mp.
37 tizolemide.mp.

38 (torsemide or "bm 02015" or "bm 2015" or bm02015 or bm2015 or demadex or diuremid or "jdl 464" or jdl464 or luprac or presaril or toradiur or torem or torrem or torasemide or unat or upcard).mp.
39 (triamterene or dyrenium or dytac or urocaudal or ademin or ademine or dyren or dyrenium or dytac or iatropur or jatropur or noridyl or "nsc 77625" or nsc77625 or pterofen or pterophene or "sk and f 8542" or "skf 8542" or skf8542 or teriam or triampterene or triamterence or triamterens or triamteril or triteren or uretren or urocaudal).mp.
40 (trichloromethiazide or aquazide or dichloromethylhydrochlorothiazide or diurese or esmarin or eurinol or fluitran or flutra or gangesol or hydrotrichlorothiazide or metahydrin or methahydrin or naqua or naquasone or salurin or triazide or trichlordiuride or trichlorex or trichlormethazide or trichlormethiazide or trichlormas or trichloromethylhydrochlorothiazide or triflumen or wadel).mp.
41 (tripamide or "adr 033" or adr033 or "e 614" or e614 or normonal).mp.
42 (xipamide or aquaforil or aquaphor or aquaphoril or aquavor or "bei 1293" or diurexan or lumitens or xipamid or xypamide or zipix).mp.
43 or/1-42
44 exp dipeptidyl carboxypeptidase inhibitor/
45 angiotensin converting enzyme inhibit*.tw.
46 (ace adj2 inhibit*).tw.
47 acei.tw.
48 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw.
49 or/44-48
50 exp angiotensin receptor antagonist/
51 (angiotensin adj3 receptor antagon*).tw.
52 (angiotensin adj3 receptor block*).tw.
53 (arb or arbs).tw.
54 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw.
55 or/50-54
56 exp calcium channel blocking agent/
57 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw.
58 (calcium adj2 (antagonist* or block* or inhibit*)).tw.
59 or/56-58
60 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.
61 (reserpine or serpentina or rauwolfia or serpasil).mp.
62 (clonidine or adesipress or arkamin or caprysin or catapres* or catasan or chlofazolin or chlophazolin or clinidine or clofelin* or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin* or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.
63 hydralazine/
64 (hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).mp.
65 or/60-64
66 exp beta adrenergic receptor blocking agent/
67 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw.

68 (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).tw.
69 or/66-68
70 exp alpha adrenergic receptor blocking agent/
71 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw.
72 (andrenergic adj2 (alpha or antagonist*)).tw.
73 ((andrenergic or alpha or receptor*) adj2 block*).tw.
74 or/70-73
75 49 or 55 or 59 or 65 or 69 or 74
76 exp hypertension/
77 (hypertens* or antihypertens*).tw.
78 ((elevat* adj2 arterial pressur*) or (elevat* adj2 blood pressur*) or (elevat* adj2 diastolic pressur*) or (elevat* adj2 systolic pressur*)).tw.
79 ((high adj2 arterial pressur*) or (high adj2 blood pressur*) or (high adj2 diastolic pressure) or (high adj2 systolic pressur*)).tw.
80 ((rais* adj2 arterial pressur*) or (rais* adj2 blood pressur*) or (rais* adj2 diastolic pressure) or (rais* adj2 systolic pressur*)).tw.
81 ((elevat* adj2 bp) or (elevat* adj2 dbp) or (elevat* adj2 sbp)).tw.
82 ((high adj2 bp) or (high adj2 dbp) or (high adj2 sbp)).tw.
83 ((rais* adj2 bp) or (rais* adj2 dbp) or (rais* adj2 sbp)).tw.
84 or/76-83
85 randomized controlled trial/
86 crossover procedure/
87 double-blind procedure/
88 (randomi* or randomly).tw.
89 (crossover* or cross-over*).tw.
90 placebo*.tw.
91 (doubl* adj blind*).tw.
92 assign*.tw.
93 allocat*.ab.
94 or/85-93
95 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
96 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/
97 (pregnancy-induced or ocular hypertens* or preeclampsia or pre-eclampsia).ti.
98 94 not (95 or 96 or 97)
99 43 and 75 and 84 and 98

Database: ClinicalTrials.gov

Search Date: 26 March 2021

Condition or disease: Hypertension
Other terms: (compared OR comparison OR versus OR vs) AND randomized
Study type: Interventional Studies (Clinical Trials)
Study Results: All Studies
Intervention/treatment: (diuretic* OR sodium chloride symporter inhibitor* OR sodium potassium chloride symporter inhibitor* OR thiazide*)

Database: WHO International Clinical Trials Registry Platform (ICTRP)

Search Date: 26 March 2021

Title: compared OR comparison OR other OR versus OR vs
Condition: Hypertension
Intervention: diuretics OR sodium chloride symporter inhibitors OR sodium potassium chloride symporter inhibitors OR thiazides
Recruitment Status: ALL

HISTORY

Protocol first published: Issue 4, 2009

Date	Event	Description
9 May 2011	Amended	New author added; minor edits to the search strategy.

CONTRIBUTIONS OF AUTHORS

Marcia Reinhart: led this review, conducted screening, extracted data, drafted review in RevMan 5, incorporated comments from fellow authors into the draft.

Lorri Puil: participated in screening, data extraction, the writing of the discussion and conclusions, and finalization of the draft.

Douglas Salzwedel: designed and executed the search strategies, participated in screening, and assisted in editing the final draft.

James M Wright: formulated the idea for the protocol, extracted data, participated in risk of bias judgments, and the writing and interpretation of the results, discussion, summary of findings tables, and conclusions.

DECLARATIONS OF INTEREST

Marcia Reinhart: Thermo Fisher Scientific (employment, since October 2020).

Lorri Puil: no relevant interests; Editor of Cochrane Hypertension but was not involved in any part of the editorial process of this review.

Douglas Salzwedel: no relevant interests; Information Specialist of Cochrane Hypertension but was not involved in any part of the editorial process of this review.

James Wright: no relevant interests; Co-ordinating Editor of Cochrane Hypertension but was not involved in any part of the editorial process of this review.

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External sources

- British Columbia Ministry of Health, Canada

  Infrastructure grant to our parent organization, the Therapeutics Initiative

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our review methods were updated to reflect the latest Cochrane methodology. The section Data collection and analysis was reported under the following subheadings: 'Selection of studies', 'Data extraction and management', 'Assessment of risk of bias in included studies', 'Measures of treatment effect', 'Unit of analysis issues', 'Dealing with missing data', 'Assessment of heterogeneity', 'Assessment of reporting biases', 'Data synthesis', 'Subgroup analysis', 'Sensitivity analysis' and 'Summary of findings and assessment of the certainty of evidence'.

In the original protocol spironolactone was included as a potassium-sparing diuretic that would be allowed in combination with a thiazide. We now realize that this was incorrect as spironolactone has proven blood pressure-lowering effects (Batterink 2010). It is no longer included under Types of interventions.

Total congestive heart failure events was added as a separate primary outcome of interest in the review. This was added after a significant difference in this outcome was noted for the comparison of calcium channel blockers with diuretics in a separate Cochrane Review (Chen 2018). We also included 'direct renin inhibitors' as a comparator drug class.

A separate sensitivity analysis was conducted excluding the ALLHAT 2000/2002 trial, as this was the largest trial and it might have had substantial influence over several meta-analyses. The inclusion of ALLHAT 2000/2002 also prevented an overall comparison (i.e. diuretics versus all other classes) as the diuretic arm would be included in the meta-analysis multiple times. Overall comparisons were therefore undertaken after the exclusion of ALLHAT 2000/2002 in sensitivity analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [adverse effects]; Angiotensin Receptor Antagonists [adverse effects]; Angiotensin-Converting Enzyme Inhibitors [adverse effects]; Antihypertensive Agents [adverse effects]; Calcium Channel Blockers [adverse effects]; *Coronary Disease; *Diabetes Mellitus, Type 2 [drug therapy]; Diuretics [adverse effects]; *Heart Failure [drug therapy]; *Hypertension [chemically induced]; *Stroke [drug therapy]; Thiazides [adverse effects]

MeSH check words

Aged; Female; Humans; Male; Middle Aged