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Eplerenone for hypertension (Review)

Tam TSC, Wu MHY, Masson SC, Tsang MP, Stabler SN, Kinkade A, Tung A, Tejani AM

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[Intervention Review]

Eplerenone for hypertension

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ABSTRACT

Background

Eplerenone is an aldosterone receptor blocker that is chemically derived from spironolactone. In Canada, it is indicated for use as adjunctive therapy to reduce mortality for heart failure patients with New York Heart Association (NYHA) class II systolic chronic heart failure and left ventricular systolic dysfunction. It is also used as adjunctive therapy for patients with heart failure following myocardial infarction. Additionally, it is indicated for the treatment of mild and moderate essential hypertension for patients who cannot be treated adequately with other agents. It is important to determine the clinical impact of all antihypertensive medications, including aldosterone antagonists, to support their continued use in essential hypertension. No previous systematic reviews have evaluated the effect of eplerenone on cardiovascular morbidity, mortality, and magnitude of blood pressure lowering in patients with hypertension.

Objectives

To assess the effects of eplerenone monotherapy versus placebo for primary hypertension in adults. Outcomes of interest were all-cause mortality, cardiovascular events (fatal or non-fatal myocardial infarction), cerebrovascular events (fatal or non fatal strokes), adverse events or withdrawals due to adverse events, and systolic and diastolic blood pressure.

Search methods

We searched the Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE, Embase, and two trials registers up to 3 March 2016. We handsearched references from retrieved studies to identify any studies missed in the initial search. We also searched for unpublished data by contacting the corresponding authors of the included studies and pharmaceutical companies involved in conducting studies on eplerenone monotherapy in primary hypertension. The search had no language restrictions.

Selection criteria

We selected randomized placebo-controlled trials studying adult patients with primary hypertension. We excluded studies in people with secondary or gestational hypertension and studies where participants were receiving multiple antihypertensives.

Data collection and analysis

Three review authors independently reviewed the search results for studies meeting our criteria. Three review authors independently extracted data and assessed trial quality using a standardized data extraction form. A fourth independent review author resolved discrepancies or disagreements. We performed data extraction and synthesis using a standardized format on Covidence. We conducted data analysis using Review Manager 5.

Main results

A total of 1437 adult patients participated in the five randomized parallel group studies, with treatment durations ranging from 8 to 16 weeks. The daily doses of eplerenone ranged from 25 mg to 400 mg daily. Meta-analysis of these studies showed a reduction in systolic blood pressure of 9.21 mmHg (95% CI −11.08 to −7.34; I^2 = 58%) and a reduction of diastolic pressure of 4.18 mmHg (95% CI −5.03 to −3.33; I^2 = 0%) (moderate quality evidence).

There may be a dose response effect for eplerenone in the reduction in systolic blood pressure at doses of 400 mg/day. However, this finding is uncertain, as it is based on a single included study with low quality evidence. Overall there does not appear to be a clinically important dose response in lowering systolic or diastolic blood pressure at eplerenone doses of 50 mg to 400 mg daily. There did not appear to be any differences in the number of patients who withdrew due to adverse events or the number of patients with at least one adverse event in the eplerenone group compared to placebo. However, only three of the five included studies reported adverse events. Most of the included studies were of moderate quality, as we judged multiple domains as being at unclear risk in the 'Risk of bias' assessment.

Authors' conclusions

Eplerenone 50 to 200 mg/day lowers blood pressure in people with primary hypertension by 9.21 mmHg systolic and 4.18 mmHg diastolic compared to placebo, with no difference of effect between doses of 50 mg/day to 200 mg/day. A dose of 25 mg/day did not produce a statistically significant reduction in systolic or diastolic blood pressure and there is insufficient evidence for doses above 200 mg/day. There is currently no available evidence to determine the effect of eplerenone on clinically meaningful outcomes such as mortality or morbidity in hypertensive patients. The evidence available on side effects is insufficient and of low quality, which makes it impossible to draw conclusions about potential harm associated with eplerenone treatment in hypertensive patients.

PLAIN LANGUAGE SUMMARY

Eplerenone for high blood pressure

Review question

The aim of this review was to determine the effectiveness of eplerenone for reducing blood pressure, its side effect profile, and its impact on clinically meaningful outcomes such as mortality and morbidity.

Background

Clinicians have used eplerenone to treat high blood pressure since 2002. It is important to determine the clinical impact of all antihypertensive medications used in patients to support their continued use in essential hypertension. We searched multiple databases and found five eligible studies in 1437 people who received either eplerenone or no medication in a random fashion.

Study characteristics

The doses of eplerenone used in these studies ranged from 25 mg to 400 mg daily. These studies followed patients for 8 to 16 weeks while on therapy. None of the studies reported on the clinically meaningful outcomes of eplerenone, such as whether eplerenone can reduce heart attacks, stroke, or death compared to placebo. Only three of the five studies reported on side effects.

Key results

There is currently no evidence that eplerenone has a beneficial effect on life expectancy or complications rleated to hypertension (e.g. heart attack, stroke). Evidence for risk of side effects with eplerenone is limited and of poor quality; it is difficult to tell the extent of possible harm with eplerenone versus placebo. This meta-analysis shows that eplerenone 50 to 200 mg/day reduces systolic blood pressure by approximately 9 mmHg and diastolic blood pressure by 4 mmHg compared to taking no medication.

Quality of the evidence

We judged the five included trials to be of moderate quality, as authors did not extensively describe portions of their methodology.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Eplerenone compared with placebo for primary hypertension

Patient or population: adults with primary hypertension

Settings: primary care

Intervention: eplerenone (25-400 mg)

Comparison: placebo

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
Effect on systolic blood pressure (mean difference in systolic blood pressure)	**(MD −9.21 mmHg, 95% CI −11.08 to −7.34)**	1437 (5)	⊕⊕⊕⊖ **Moderate**[a]
Effect on diastolic blood pressure (mean difference in diastolic blood pressure)	**(MD −4.18 mmHg, 95% CI −5.03 to −3.33)**	1437 (5)	⊕⊕⊕⊖ **Moderate**[a]
Any adverse event	**OR** 1.07 (0.82 to 1.41)	1105 (3)	⊕⊕⊖⊖ **Low**[a,b]
Adverse event leading to withdrawal	**OR** 1.10 (0.47 to 2.55)	1105 (3)	⊕⊕⊖⊖ **Low**[a,b]

CI: confidence interval; **OR**: odds ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded due to high risk of bias in many of the studies.
[b]Downgraded as only 3 of the included 5 trials provided data.

BACKGROUND

Description of the condition

Hypertension is associated with structural changes in the heart and blood vessels, which can lead to cardiovascular mortality and morbidity (e.g. cardiovascular disease, stroke, peripheral vascular disease, and renal disease). Hypertension is generally defined as having a systolic blood pressure (SBP) of 140 mmHg or more, a diastolic blood pressure (DBP) of 90 mmHg or more, or both (Arguedas 2009; CHEP 2015). For every 20 mmHg increase in SBP and 10 mmHg increase in DBP (through the range of 115/75 to 185/115 mmHg) in people aged 40 to 70 years, the risk of cardiovascular disease-related morbidity doubles (JNC 7). Epidemiologic studies have shown increased blood pressure to be associated with increased incidence of stroke, ischemic heart disease, and other vascular mortality (Lewington 2002). While blood pressure is a surrogate goal of therapy for the prevention of hypertension-associated target-organ damage (DiPiro 2014), no research has convincingly shown that lowering blood pressure below the target value of 140/90 mmHg reduces cardiovascular morbidity and mortality (Arguedas 2009). At present, there is no definitive threshold to predict the blood pressure above which treatment provides more benefit than harm (Arguedas 2009). In very elderly individuals aged 75 years or older, there is no established association between SBP and all-cause mortality (Banach 2014). Interestingly, there is some evidence that blood pressure values below 140/70 mmHg are associated with excess mortality in individuals aged 85 and over (Van Bemmel 2006). Current recommendations on target blood pressures are mostly based on expert opinion and cannot be generalized to all age groups (NCGC 2011). This variability underscores the importance of finding safe and effective antihypertensive agents that demonstrate a proven benefit for improving hard clinical outcomes (morbidity and mortality), rather than chasing arbitrary blood pressure values.

Description of the intervention

Eplerenone is an aldosterone receptor blocker that is chemically derived from spironolactone. In a recent Cochrane Review, spironolactone, considered fourth-line therapy for hypertension in patients already treated with multiple medications, was shown to reduce systolic/diastolic blood pressure by approximately 20/7 mmHg compared to placebo. However, the review found no evidence on the effect of spironolactone on clinical outcomes in hypertensive patients (Batterink 2010). This review attempts to define the effect of eplerenone, another aldosterone antagonist, on hard clinical outcomes in hypertensive patients.

Compared to spironolactone, eplerenone exhibits less affinity for androgen, progesterone, and glucocorticoid receptors (Katzung 2012). As a result, many authors consider that it reduces the risk of gynaecomastia, menstrual irregularities, and sexual dysfunction. Eplerenone undergoes extensive hepatic metabolism, primarily through the enzyme cytochrome P450 3A4 (CYP3A4) to inactive metabolites, so clinicians should avoid co-administration of potent CYP3A4 inhibitors (Muldowney 2009). Eplerenone itself neither induces nor inhibits CYP3A4 and does not alter the pharmacokinetics of co-administered substrates or inducers of CYP3A4, highly protein-bound drugs, or highly renally cleared drugs. As a result, dosage adjustments of other drugs are generally not necessary. Less than 5% of the administered dose is cleared unchanged in the urine and faeces. Current data suggest that adverse effects are generally rare and mild with eplerenone therapy. These include hyperkalemia, dizziness, elevation in serum creatinine, diarrhea, cough, fatigue, dyslipidemia, abdominal pain, and albuminuria (Muldowney 2009). Hyperkalemia is the most significant adverse effect of eplerenone and may result in fatal cardiac arrhythmias if serum potassium levels are inadequately monitored. Patients with declining renal function are at greater risk for hyperkalemia. Evidence also suggests that diabetic patients with proteinuria may be at increased risk of high serum potassium levels. No data is currently available for the use of eplerenone in patients with severe hepatic dysfunction, although those with mild to moderate impairment (Child-Pugh class B) do not require dosage adjustments (eCPS 2014).

Eplerenone is contraindicated in people with known hypersensitivity to the drug or its excipients, clinically significant hyperkalemia or serum potassium of more than 5.0 mmol/L at initiation of treatment, severe hepatic dysfunction (Child-Pugh class C), moderate to severe renal dysfunction (eGFR < 50 mL/min/1.73 m^2), type 2 diabetes with microalbuminuria, and in people taking potassium-sparing diuretics, potassium supplements, or potent CYP3A4 inhibitors (eCPS 2014).

In Canada, eplerenone is indicated for use as adjunctive therapy to reduce mortality for heart failure patients with New York Heart Association (NYHA) class II systolic chronic heart failure and left ventricular systolic dysfunction, and as adjunctive therapy for patients with heart failure following myocardial infarction. Additionally, it is indicated for treating mild and moderate essential hypertension in patients who cannot be treated adequately with other agents (eCPS 2014). The Canadian Hypertension Education Program (CHEP) recommends using aldosterone antagonists as adjuncts for patients with systolic dysfunction (ejection fraction < 40%) and recent cardiovascular hospitalization, acute myocardial infarction, elevated brain-type natriuretic peptide (BNP) or N-terminal pro b-type BNP (NT-proBNP) level, or NYHA class II to IV symptoms (CHEP 2015). The American Society of Hypertension recommends the addition of aldosterone antagonists when standard three-drug regimens (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker/calcium channel blocker/diuretic) are ineffective in treatment-resistant patients (Weber 2014).

How the intervention might work

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathophysiology of hypertension. Aldosterone increases blood pressure by inducing sodium reabsorption, vascular remodeling, and endothelial dysfunction, and possibly through other genomic and non-genomic effects (eCPS 2014). The role of aldosterone itself has been established not only in hypertension secondary to hyperaldosteronism, but also in primary, or essential, hypertension. There is also some evidence that non-hypertensive patients with high-normal aldosterone levels are at increased risk for developing elevated blood pressure (Jansen 2009). Eplerenone is an aldosterone antagonist and competes with aldosterone for binding to the mineralocorticoid receptor. In the late distal and cortical collecting tubules of the kidney, this antagonism will lead to decreased activation of sodium channels and decreased numbers of sodium/potassium ATPase pumps. The net effect is diuresis: increased sodium and, as a consequence, water excretion (Katzung 2012).

Aldosterone antagonists may also have a role in treatment-resistant hypertension. Non-responders to typical antihypertensive therapies may benefit from a trial of an aldosterone antagonist (Weber 2014). Prolonged treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which initially lower serum aldosterone levels, may result in a rebound increase in serum aldosterone to higher than pre-treatment levels. This is referred to as 'aldosterone escape' or 'aldosterone breakthrough' and could be a key mechanism in resistance to ACE inhibitors and ARBs (Jansen 2009).

Aldosterone has also been implicated in blood pressure-independent adverse events, including vascular inflammation and cardiac and perivascular fibrosis, which may promote end-organ damage. Evidence suggests that patients with hyperaldosteronism may be at increased risk for stroke, non-fatal myocardial infarction, atrial fibrillation, elevated left ventricular mass, and arterial wall stiffness versus matched controls with essential hypertension (Jansen 2009). Use of an aldosterone antagonist may thus reduce these pathologies in at-risk patients.

Why it is important to do this review

Hypertension can be difficult to manage. Patients may be intolerant to antihypertensive medications, and many require multiple classes of medications to control their blood pressure. More importantly, lowering blood pressure below 140/90 mmHg is not a validated surrogate outcome for clinically significant endpoints such as mortality and morbidity. It is important to determine the clinical impact of all antihypertensive medications, including aldosterone antagonists, to support their continued use in essential hypertension. Previous systematic reviews have not evaluated the effect of eplerenone on cardiovascular morbidity, mortality, and magnitude of blood pressure lowering in people with hypertension (Wright 2009).

OBJECTIVES

To assess the effects of eplerenone monotherapy versus placebo for primary hypertension in adults. Outcomes of interest were all-cause mortality, cardiovascular events (fatal or non-fatal myocardial infarction), cerebrovascular events (fatal or non fatal strokes), adverse events or withdrawals due to adverse events, and systolic and diastolic blood pressure.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials that compare oral eplerenone monotherapy to placebo.

Types of participants

Trials including participants of both sexes older than 18 years of age with primary hypertension defined by SBP greater than 140 mmHg, DBP greater than 90 mmHg, or both, with no known secondary cause for the high blood pressure. We included trials involving participants with and without co-morbidities.

Types of interventions

The intervention of interest was oral eplerenone monotherapy (at any dose). The comparative intervention was placebo.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Cardiovascular mortality
- Non-cardiovascular mortality
- Number of patients experiencing at least one serious adverse event
- Fatal and non-fatal, disabling stroke
- Fatal and non-fatal myocardial infarction

Secondary outcomes

- Number of patients with at least one adverse event
- Number of patients who withdrew due to adverse events
- Change blood pressure
  - Change in systolic blood pressure
  - Change in diastolic blood pressure

Search methods for identification of studies

Electronic searches

We searched the following databases for primary studies.

- Cochrane Hypertension Specialised Register (searched 3 March 2016).
- Cochrane Register of Controlled Trials (CENTRAL; 2016, Issue 3) via the Cochrane Register of Studies Online (searched 3 March 2016).
- MEDLINE Ovid (1946 to 3 March 2016).
- Embase Ovid (1974 to 3 March 2016).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 3 May 2016).

The Cochrane Hypertension Specialised Register includes controlled trials from searches of CENTRAL, MEDLINE, Embase, CAB Abstracts, CINAHL, Food Science and Technology Abstracts (FSTA), Global Health, LILACS,ProQuest Dissertations & Theses, PsycINFO, the Web of Science, and the WHO International Clinical Trials Registry Platform (ICTRP).

We searched electronic databases using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected medical subject headings (MeSH) and free text words. We used no language restrictions and translated the MEDLINE search strategy into the other databases using the appropriate controlled vocabulary as applicable. We present full strategies in Appendix 1.

Searching other resources

We also tried to collect information from the following additional resources.

1. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

2. Reference lists of all papers and relevant reviews identified.
3. Authors of relevant papers, regarding any further published or unpublished work.
4. Authors of trials reporting incomplete information, to obtain the missing information.
5. ISI Web of Science for papers that cite studies included in the review.
6. European Medicines Agency Database.
7. United States Food and Drug Administration (FDA) Database.
8. Manufacturer of eplerenone.
9. Database of Abstracts of Reviews of Effectiveness (DARE), for related reviews.

Data collection and analysis

Selection of studies

Three review authors (SM, TT, MW) independently assessed all identified studies to determine whether they met the predefined inclusion criteria. We reviewed all references identified in the search that mentioned the use of eplerenone and included them if they met the criteria. We documented reasons for excluding studies and resolved any differences regarding inclusion through discussion with a fourth independent review author.

Data extraction and management

Once we identified all studies, three independent review authors examined those that fulfilled the inclusion criteria in detail. We used a web-based systematic review program, Covidence, to create a standardized data extraction form.

Assessment of risk of bias in included studies

We assessed the following parameters.

- Method of random sequence generation.
- Method of allocation concealment.
- Blinding to treatment allocation (including healthcare provider, assessor, and patient).
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Funding of clinical trial.

We resolved any differences in interpretation of the data through consensus. If additional information was required, we contacted the original authors of the study and then reassessed the study once the missing information was available, where possible. Three review authors independently collected study characteristics and the outcome measures of interest using a pre-formulated data extraction sheet on Covidence. We collected all data, regardless of compliance or completion of follow-up, in order to allow for intention-to-treat analysis.

Measures of treatment effect

For evaluation of the primary outcomes (all-cause mortality, cardiovascular events, and cerebrovascular events), we planned to record the total number of patients with at least one event within each trial, calculating proportions for these dichotomous outcomes and presenting comparisons between groups as relative risk ratios (RRs) with corresponding 95% confidence intervals (CIs).

We planned to combine data for blood pressure reduction using a weighted mean difference method. This combines a weight based on the number of individuals in the trial and the within-study variance. If the trial did not report the within-study variance for decrease in blood pressure, we imputed the standard deviation (SD) from the average SD from the other trials.

We first performed all analyses using a fixed-effect model.

Unit of analysis issues

We used data from all patients individually randomized to each intervention in the analyses, taking care to identify situations in which studies had censored/excluded data and to differentiate data presented as the total number of events or the total number of patients with a first event. We contacted authors for clarification if necessary. We intended to calculate proportions for the first relevant event that occurred for each patient randomized to a particular intervention.

Dealing with missing data

In general if there were missing data, we contacted the authors of the study for clarification and documented this process. If we could not obtain the SD of the change in blood pressure, we imputed the value (using SD of the change data from other similar trials).

Assessment of heterogeneity

We assessed heterogeneity across the studies using the I^2 statistic (defining important heterogeneity at a threshold of 30% to 60%) and the Chi^2 statistic (with statistical significance set at $P < 0.10$). Where we did not detect heterogeneity, we used a fixed-effect model. Otherwise, we used a random-effects model to determine if the effects of eplerenone changed depending on the analysis model. More importantly, we planned to explore clinical and methodological sources of heterogeneity, considering characteristics like: baseline risk factors for the outcomes of interest, duration of studies, age, race, and sex distribution of participants across the studies. Based on the exploration of sources of heterogeneity, we made decisions about the appropriateness of meta-analyzing data.

Assessment of reporting biases

In the event that we assumed that missing data represented a poor outcome, or where we imputed data, we planned to carry out sensitivity analyses to see if results were sensitive to the assumptions being made. However, since we did not find any clinical outcome data, this type of imputation was not necessary.

Data synthesis

We used Cochrane Review Manager 5 (RevMan 5) software , for all data analyses. We based quantitative analyses of outcomes on intention-to-treat results. We used RRs and the fixed-effect or random-effects model (depending on heterogeneity results) to combine outcomes across trials. We calculated absolute risk reduction (ARR) as risk difference × 100, and the numbers needed to treat for an additional beneficial outcome (NNTB) as 1/risk difference for all dichotomous outcomes. We pooled data for blood pressure reduction using a weighted mean difference method with standard deviations.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following four subgroup analyses.

1. Trials of less than 6 months' duration, of 6 to 12 months' duration, and of more than 12 months' duration.
2. Effect of ethnic group on blood pressure and adverse events.
3. Effect of age on blood pressure and adverse events.
4. Effect of dose on blood pressure and adverse events.

Sensitivity analysis

We planned to carry out sensitivity analyses in order to test for the robustness of the results. We intended to analyze the following categories separately.

1. Trials without proper randomization compared to those with proper randomization.
2. Trials performed without proper allocation concealment versus those with proper allocation concealment.
3. Unblinded versus blinded trials.
4. Inclusion versus exclusion of data from trials where we imputed blood pressure standard deviations.

RESULTS

Description of studies

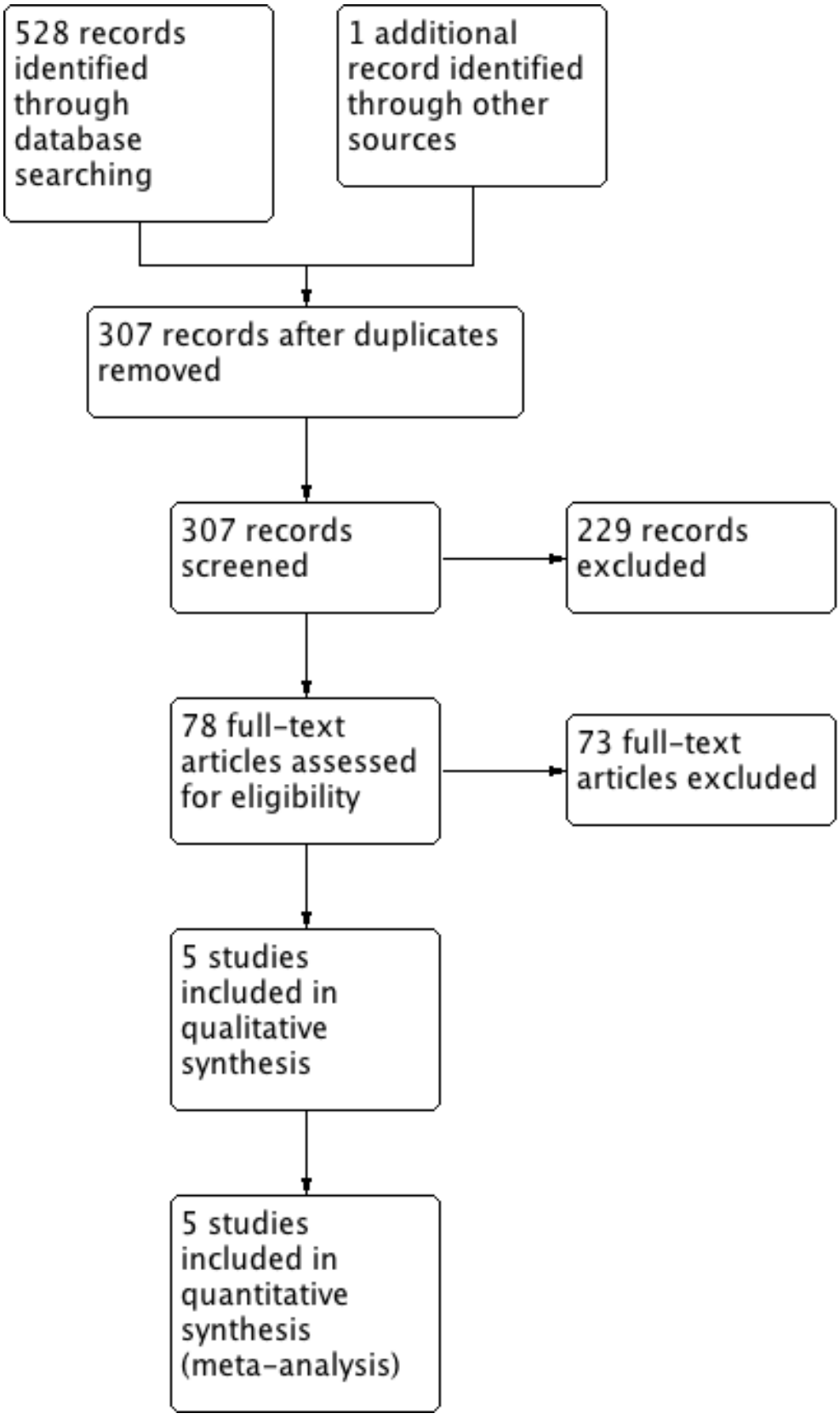
See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search strategy identified 307 citations in CENTRAL, MEDLINE, and Embase. Following a review of their titles and abstracts, we excluded 229 citations that obviously did not meet our inclusion criteria and selected 78 studies for further review. We reviewed the full text of these 78 studies and excluded 73 that did not meet our inclusion criteria.

Of the six citations that met our inclusion criteria, one proved to be a duplicate publication, leaving five unique trials that met our inclusion criteria. See Figure 1.

Figure 1. Study flow diagram.



Included studies

Refer to Characteristics of included studies for further details regarding the studies.

All five included studies were parallel-group, randomized controlled trials. Together, they involved a total of 1437 participants, who received treatment for 8 to 16 weeks. The daily doses of eplerenone ranged from 25 mg to 400 mg. Participants' average age was 54 years, and there were slightly more men than women (64%). The mean baseline blood pressure (BP) in the eplerenone group was 153/101 mmHg, compared to 152/100 mmHg in the placebo group.

Excluded studies

See: Characteristics of excluded studies.

We excluded 73 trials for the following reasons.

1. Not a randomized controlled trial (k = 32).
2. Did not study patients with essential hypertension (k = 16).
3. Treatment arm was not eplerenone monotherapy (k = 9).
4. Compared eplerenone with other antihypertensive agents (k = 7).
5. Did not study any of our primary or secondary outcomes of interest (k = 5).
6. Terminated study on clinicaltrials.gov; efforts to contact the responsible party were fruitless in obtaining usable information for the meta-analysis (k = 1, NCT01373086).
7. Completed study on clinicaltrials.gov but with no published results; efforts to contact the responsible party were fruitless in obtaining usable information for the meta-analysis (k = 1, NCT02345044).
8. Unpublished trial not providing enough information to be used in the analysis (k = 1, Trial 015 1999); found through the FDA medical reviews on the approval of eplerenone.

Risk of bias in included studies

We assessed the risk of bias on the basis of five major criteria: allocation concealment, blinding, completeness of outcome data addressed, presence of selective reporting, and other potential sources of bias (see Figure 2). Three review authors (SM, TT, MW) independently performed the 'Risk of bias' assessment on Covidence, resolving any differences in interpretation of the data through consensus with a fourth review author (AT). If additional information was required, we contacted the original author of the study and reassessed the study in light of the availability of missing information. We summarize our contact with the original authors of the five included studies in Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

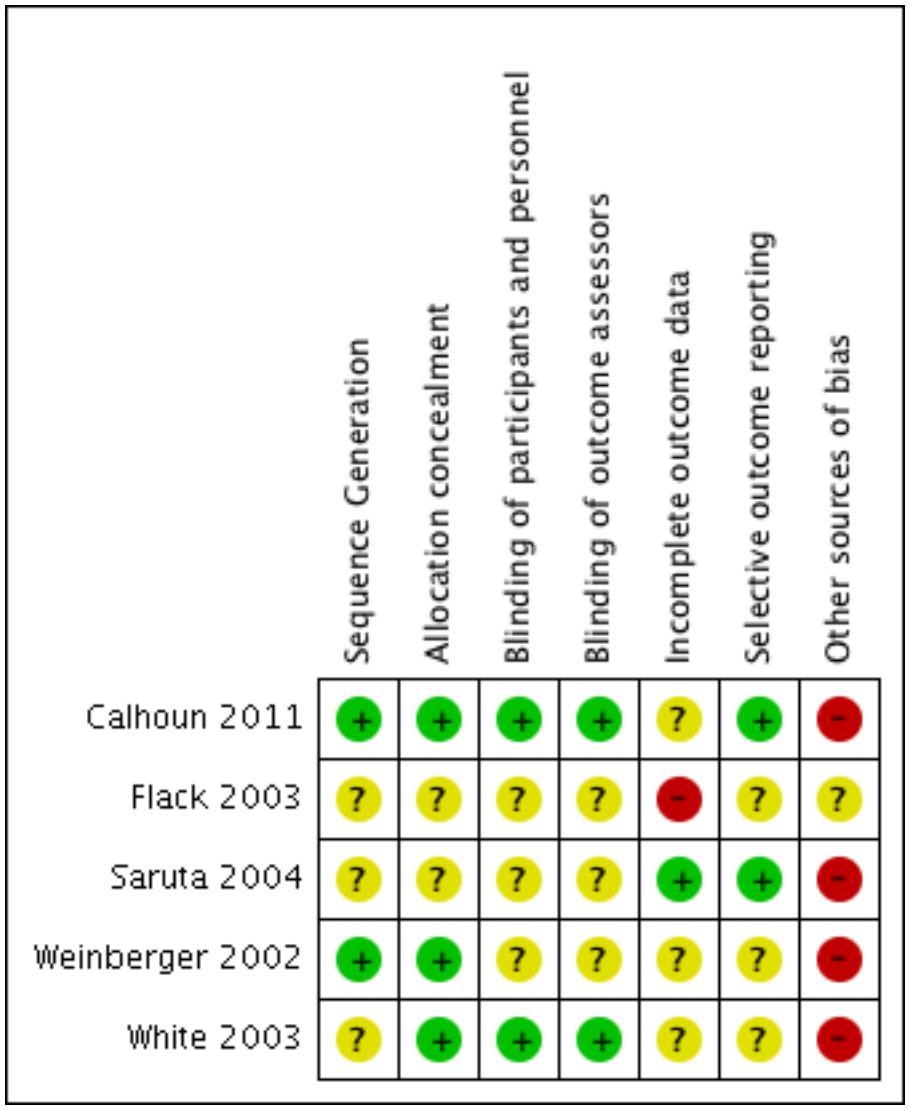


Figure 3. Summary of data extraction and contact with corresponding authors

Study ID	Outcomes of Interest					Protocol	Study Author Contact	Contact Record
	Primary Outcome	SBP	DBP	Any AE	Withdrawal due to AE			
Calhoun 2011	X	√	√	O	O	☐ Retrieved √ Information from trials registry ☐ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Jan 1, 2016
Flack 2003	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Jan 3, 2016
Saruta 2004	X	√	√	O	O	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Nov 14, 2015
Weinberger 2002	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Jan 3, 2016
White 2003	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data √ No additional data ☐ No response ☐ N/A	Email Jan 3, 2016 (wwhite@uchc.edu) - clarification re: trial methods

√ Full reporting of results for treatment comparison of interest
X No reporting
O Partial reporting of results (i.e., only p-value, "non-significant")

Allocation

Calhoun 2011 reported performing allocation by generating randomization sequences using an interactive voice-response system provider. A validated system automated the random assignment of participant numbers to randomization numbers, linking them to the different treatment groups and the medication numbers on treatment packs. Study drugs were identical in packaging, labeling, schedule of administration, appearance, taste, and odor in order to conceal the nature of the treatment.

Flack 2003 and Saruta 2004 did not describe methods of allocation concealment; the trial reports noted that the order in which participants received eplerenone and placebo was randomized; however, authors did not describe the method for randomization or respond to our attempts to contact them.

Weinberger 2002 allocated all participants at the same time as randomization after the run-in period by using a randomized computer-generated schedule for sequence generation.

White 2003 stated that the study coordinator performed allocation concealment via an interactive voice response system. Through email contact, the primary author of White 2003 clarified details on the randomization of the participants, which investigators accomplished using standard multicenter block randomization techniques.

Blinding

Flack 2003, Saruta 2004, and Weinberger 2002 described blinding methods poorly, stating that they conducted double-blind trials but without describing how blinding was maintained beyond use of a placebo pill. Thus, the information available for assessing the appropriateness of blinding in these studies was inadequate.

Only two of the five studies adequately described blinding of participants and outcome assessors (Calhoun 2011; White 2003). Calhoun 2011 stated that participants, investigators, outcome assessors, and data analysts remained blinded to treatment assignments. Moreover, study drugs were identical in packaging, labeling, schedule of administration, appearance, taste, and odor in order to conceal the nature of the treatment.

Additional correspondence with White 2003 served to clarify details on the blinding of the study participants and outcome assessors. White 2003 stated both study participants and site staff were blinded to treatment assignment. The study medication was in bottles of unidentified investigational product and was sent from a central location, so the outcome assessors had no way of knowing the randomization medication or code.

Incomplete outcome data

Only one of the five included studies adequately reported how they dealt with incomplete outcome data (Saruta 2004). In this case, Saruta 2004 excluded one participant in the eplerenone 50 mg group from the efficacy analysis due to withdrawal of consent. The results in a group of 49 participants are unlikely to be affected by missing data from 1 participant.

However, there was a high risk of bias in Flack 2003. Four participants in the placebo and 8 participants in the eplerenone group had no post baseline assessment and were not included in the efficacy analysis. In addition, 41% of participants withdrew from the placebo group, compared to 26% in the eplerenone group, and authors did not describe details of imputing missing values using the last observation carried forward method. The high rates of withdrawal in the placebo group may cause smaller mean changes in blood pressure and thus exaggerate the effects seen in the eplerenone group.

The remaining three included studies were at unclear risk of bias for incomplete outcome data reporting. In White 2003, there was insufficient reporting of incomplete outcome data. Other than treatment failure, the authors did not specify the other reasons for withdrawals in each treatment group and how they accounted for missing data in the primary outcomes. There was not enough information to assess the risk of bias due to incomplete outcome data.

In Weinberger 2002, eight participants were not included in the efficacy analyses. In addition, 39 participants did not complete the study. The authors of Weinberger 2002 did not specify how withdrawals were distributed across groups or how authors dealt with missing data.

In Calhoun 2011, the percentage of withdrawals from treatment groups ranged from 6.8% to 13.0%. The authors did not thoroughly document reasons for withdrawal but noted that they conducted all efficacy analyses with the full analysis set and imputed missing measurements by carrying forward the last available observation. However, there was not enough available information to assess the risk of bias from the missing data.

Selective reporting

In most of the included studies, there did not seem be selective reporting of outcomes (Calhoun 2011; Flack 2003; Saruta 2004).

Calhoun 2011 reported all outcomes specified in their protocol registered on ClinicalTrials.gov. Flack 2003 reported all primary study outcomes but failed to report some secondary endpoints and serious adverse events. Weinberger 2002 and White 2003 reported all outcomes specified in the Methods section. However, there was no protocol available to assess the a priori design.

It is worth noting that none of the included studies reported clinically meaningful outcomes (i.e. any of our primary outcomes) related to hypertension. Thus, there may be a high risk of selective reporting based on the omission of outcomes that should inform clinical practice and be collected in clinical trials involving human participants (e.g. all-cause mortality, serious adverse events).

Other potential sources of bias

Four of the five included studies received industry funding. Pharmacia Corporation, which Pfizer purchased in 2002, financed Weinberger 2002, and Pfizer Inc funded Saruta 2004. Novartis funded Calhoun 2011, which academic authors and Novartis Parma designed together. Novartis was also responsible for collecting data from investigational sites to create the clinical database for the data analysis. As per the additional information provided by the corresponding author, Pharmacia Corporation sponsored White 2003.

Flack 2003 did not report the source of funding.

Effects of interventions

See: **Summary of findings for the main comparison**

See: Summary of findings for the main comparison.

Primary outcomes

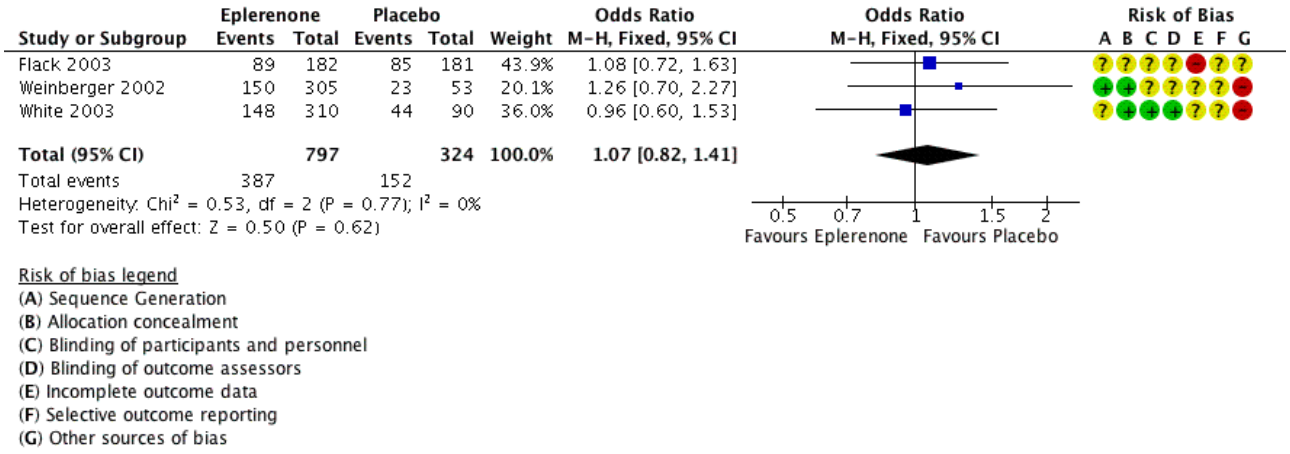
Unfortunately, none of the included studies reported results for the following clinical outcomes: all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, serious adverse events, fatal and non-fatal myocardial infarction, or fatal and non-fatal stroke.

Secondary outcomes

Number of participants with at least one adverse event

There was no difference in the incidence of participants experiencing any adverse event in three trials(Flack 2003; Weinberger 2002; White 2003; Analysis 1.1; Figure 4). However, we could not stratify these results based on dose, and the potential harms associated with increased daily doses of eplerenone are uncertain. We did not specifically assess rates of hyperkalemia in this review but will do so in future updates.

Figure 4. Forest plot of comparison: 29 Eplerenone Monotherapy vs Placebo, outcome: Any Adverse Event.



Number of participants who withdrew due to adverse events

There was no difference in the incidence of adverse events leading to discontinuation in the eplerenone group compared to placebo (Flack 2003; Weinberger 2002; White 2003; Analysis 1.2).

Change in blood pressure

Four studies reported mean systolic and diastolic blood pressures from participants who were seated (Calhoun 2011; Saruta 2004; Weinberger 2002; White 2003). Flack 2003 measured participants blood pressure while standing/supine, which could have raised/lowered the reading with respect to the other studies. Ideally, all studies would have reported blood pressures measured in the same position.

White 2003 studied four different daily doses of eplerenone (25 mg, 50 mg, 100 mg, and 200 mg). We used the mean change from baseline in seated blood pressure in our analysis, and we extracted data from Figure 1 in the published study report. The authors did not specify whether the error bars presented in Figure 1 in the published study report were standard deviations or standard errors. Using graphing methods, we estimated the variances in Figure 1 based on the pictorial error bars. Comparing these variances with the other studies, we assumed they were standard errors, as the numbers were similar. We felt this to be an appropriate estimate, as authors reported changes from baseline in daytime and nighttime blood pressures in Table 2 in the published study report as standard errors with similar numbers. When inputting our data for analysis, we distributed the sample size of the placebo group equally among the four different treatment groups.

Weinberger 2002 studied three different daily doses of eplerenone (50 mg, 100 mg, and 400 mg). The authors reported the change from baseline in systolic and diastolic blood pressure in seated position in Figure 1 in the published study report. Using the same assumptions and methods described in White 2003, we estimated the variance numbers from the error bars in Figure 1 in the published study report and assumed them to be standard errors in our calculations. Again, we distributed the sample size of the placebo group equally among the three different treatment groups when inputting our data for analysis.

Saruta 2004 studied three different daily doses of eplerenone (50 mg, 100 mg, and 200 mg). The mean change in cuff seated systolic and diastolic blood pressure from baseline was extracted from Figure 1 in the published study report. We estimated the variance as we did in White 2003 and Weinberger 2002. We felt this to be an appropriate estimate, as adjusted mean change in pulse pressure, presented in Table 2 in the published study report, showed variance with similar numbers and were reported as standard errors. Similarly to White 2003 and Weinberger 2002, we distributed the sample size of the placebo group equally among the three different treatment groups when inputting our data for analysis.

Flack 2003 reported mean changes in systolic and diastolic blood pressure but did not specify the position or method of blood pressure monitoring. Flack 2003 studied eplerenone 50 mg/day

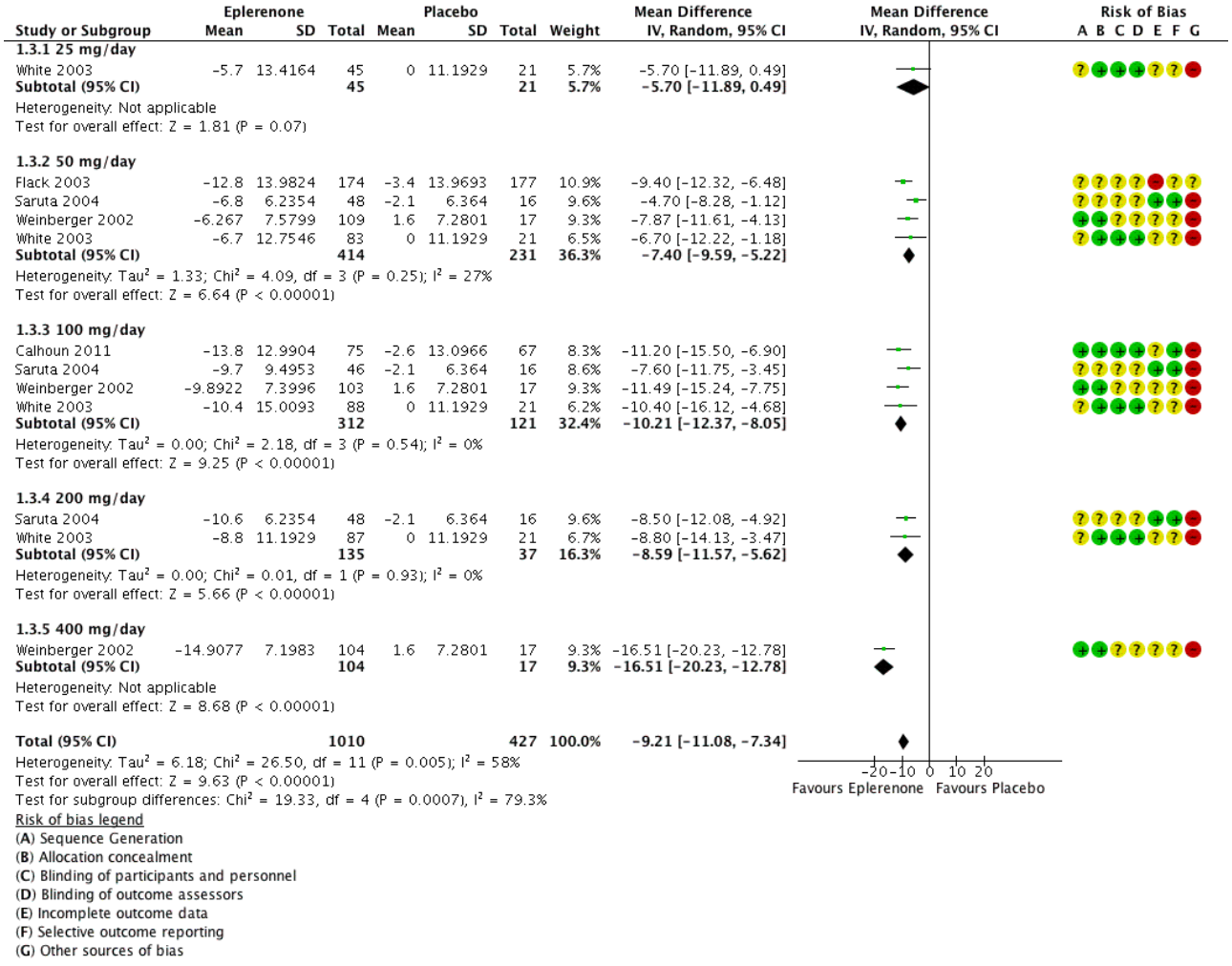
against placebo. We used the data presented in Table 3 in the published study report of the mean changes in SBP and DBP for placebo and eplerenone for all participants. Calhoun 2011 reported mean changes in sitting systolic and diastolic blood pressures, comparing the daily dose of 100 mg against placebo. Using the data presented in Figure 3 in the published study report, we used graphing methods in the bar graph to estimate standard errors. We did not need to distribute the sample size of the placebo group in Flack 2003 and Calhoun 2011 because only one eplerenone treatment group was used in their analyses.

We performed meta-analysis of the blood pressure lowering effects of eplerenone versus placebo for the five included studies (Calhoun 2011; Flack 2003; Saruta 2004; Weinberger 2002; White 2003). There were a total of 1437 participants receiving eplerenone or placebo in parallel group randomized controlled trials. The duration that participants were in these trials ranged from 8 to 16 weeks.

Change in systolic blood pressure

The analysis of the mean difference in SBP showed that eplerenone reduced SBP by 9.21 mmHg (95% CI −11.08 to −7.34; P < 0.001; Analysis 1.3; Figure 5). There appears to be moderate heterogeneity in the results (I^2 = 58%).

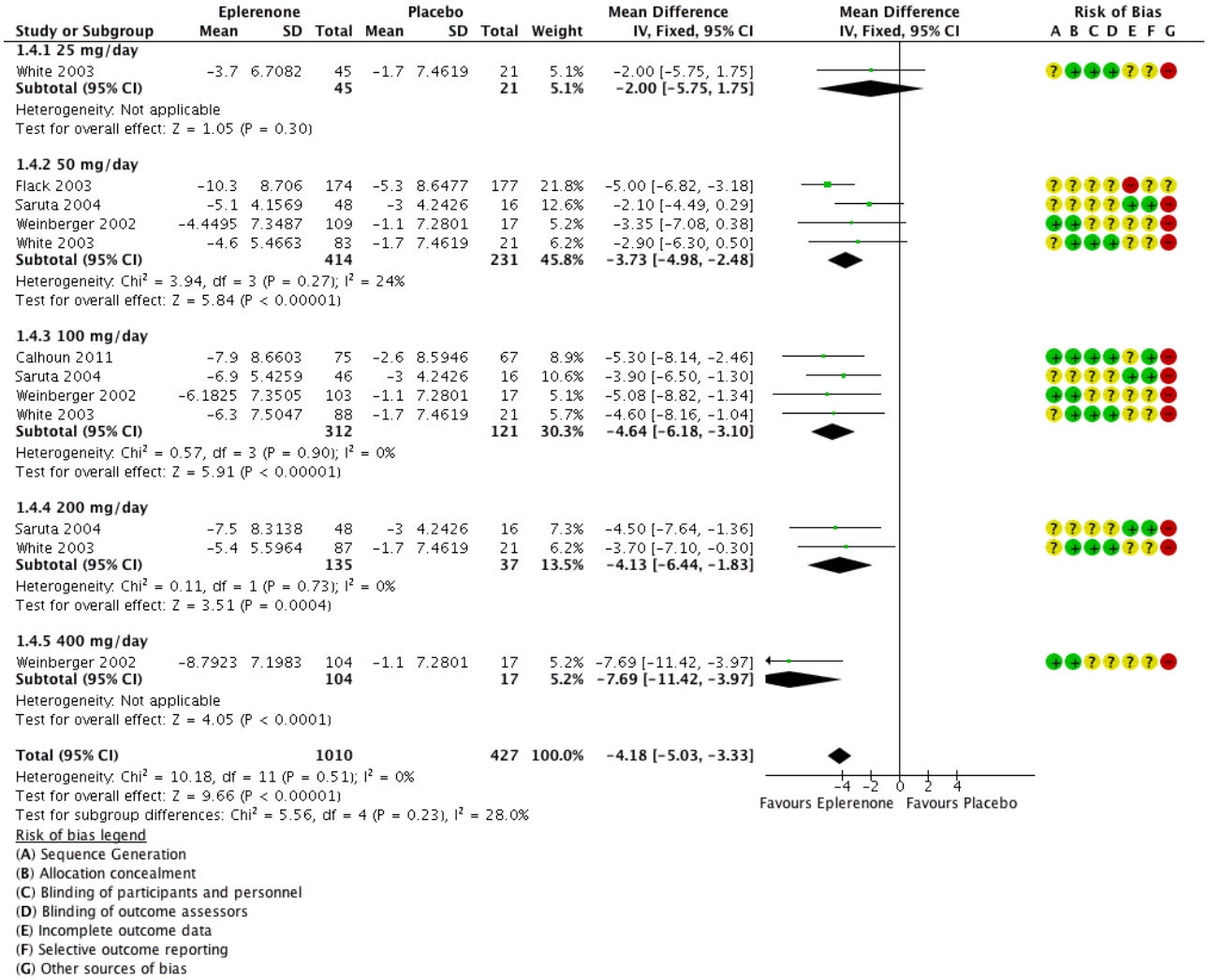
Figure 5. Forest plot of comparison: 1 Eplerenone monotherapy vs placebo, outcome: 1.3 Systolic blood pressure.



Change in diastolic blood pressure

The analysis of the mean difference in DBP found that eplerenone reduced DBP by 4.18 mmHg (95% CI −5.03 to −3.33; P < 0.001; Analysis 1.4; Figure 6). There was no statistical heterogeneity in the results (I^2 = 0%) when using a fixed-effect model. We summarize the results in the Summary of findings for the main comparison.

Figure 6. Forest plot of comparison: 1 Eplerenone monotherapy vs placebo, outcome: 1.4 Diastolic blood pressure.



Subgroup analyses

Because all five included studies were of short duration, there was insufficient evidence to perform a subgroup analysis of trials of less than 6 months' duration, 6 to 12 months' duration, and more than 12 months' duration. There was also no information provided on the blood pressure lowering effects of participants in different age groups, so a subgroup analysis was not possible. Only one study analyzed the effect of ethnicity on blood pressure (Flack 2003), so we did not perform a subgroup analysis on its influence as an effect modifier.

However, due to the variation in doses used in the included studies, we could stratify blood pressure data by dose in the meta-analysis in order to examine the possibility of a dose response. For mean changes of both systolic and diastolic blood pressure, eplerenone 25 mg/day did not have a statistically significantly effect.

For changes in systolic blood pressure, the confidence intervals overlapped at eplerenone doses of 50 mg/day to 200 mg/day. However, eplerenone 400 mg/day decreased mean systolic blood pressure by 16.5 mmHg (95% CI −20.23 to −12.78; Analysis 1.3.5), which does not overlap with any other doses studied. This may lead us to believe eplerenone does exhibit a dose response at doses of 400 mg/day or higher. However, these data were only available from Weinberger 2002 as none of the other authors explored doses higher than 200 mg/day. Since only one study at high risk of bias investigated this dose, we cannot be confident of this effect until other studies replicate it.

The confidence intervals for change in DBP all overlapped at eplerenone doses of 50 mg/day to 400 mg/day. Thus, there is no apparent dose response. In other words, doses of 400 mg/day will not lower diastolic blood pressure more than doses of 50 mg/day (Analysis 2.2).

Interestingly, when we exclude the results from Weinberger 2002's analysis with 400 mg/day, there is no heterogeneity (I^2 = 5%) with our results in changes in systolic blood pressure. In addition, when we exclude the 100 mg daily dose of Weinberger 2002, the I^2 decreases to 0%. There may be some unknown factor that is contributing to the heterogeneity of the results we found with changes in systolic blood pressure that is inherent in Weinberger 2002 study. We could not identify any apparent reason for heterogeneity based on our analysis of risk of bias, characteristics

of included participants, or specifics of interventions tested. When we changed the analysis from a fixed-effect model to a random-effects model to test the robustness of the finding, the point estimate and confidence interval for SBP reduction did not change substantially (−9.21 mmHg, 95% CI −11.08 to −7.34; Analysis 1.3).

We conducted additional dose response comparisons based on dose comparisons within trials (Analysis 2.1; Analysis 2.2). Readers should be cautious of drawing definitive conclusions from these comparisons, as at best, three trials made the same dose-to-dose comparisons and at worst, one trial compared a particular dose-to-dose comparison. With these qualifications in mind, we can make some general observations.

SBP direct dose comparisons

See Analysis 2.1.

- It appears that 100 mg/day of eplerenone reduces SBP more than 50 mg/day eplerenone by 4.27 mmHg (95% CI −5.94 to −2.61), based on three trials with low statistical heterogeneity. These differences in SBP are within the variability of BP measurements and are unlikely to be clinically important (Musini 2009).
- It is possible that 400 mg/day of eplerenone reduces SBP more than 50 mg/day or 100 mg/day of eplerenone based on one experiment at unclear risk of bias. These differences in SBP are within the variability of BP measurements and are unlikely to be clinically important (Musini 2009).
- The difference in SBP reduction between 200 mg/day and 50 mg/day of eplerenone is unclear. One experiment demonstrated a significant difference while another experiment demonstrated no difference in SBP reductions with 200 mg/day versus 50 mg/day (high statistical heterogeneity).
- Two experiments showed no statistical difference in SBP reduction between 200 mg/day and 100 mg/day of eplerenone (no statistical heterogeneity).

DBP direct dose comparisons

See Analysis 2.2.

- It appears that 100 mg/day of eplerenone reduces DBP by 1.74 mmHg more than 50 mg/day eplerenone (Analysis 2.1), based on three trials with low statistical heterogeneity. These differences in SBP are within the variability of BP measurements and are unlikely to be clinically important (Musini 2009).
- It is possible that 400 mg/day of eplerenone reduces DBP more than 50 mg/day or 100 mg/day of eplerenone based on one experiment with unclear risk of bias. These differences in SBP are within the variability of BP measurements and are unlikely to be clinically important (Musini 2009).
- The difference in DBP reduction between 200 mg/day and 50 mg/day of eplerenone is unclear. One experiment demonstrated a numerical difference (not statistically significant) while another experiment demonstrated no difference in lowering SBP with 200 mg/day versus 50 mg/day (high statistical heterogeneity).
- Two experiments showed no statistical difference in SBP reduction between 200 mg/day and 100 mg/day of eplerenone (no statistical heterogeneity).
- One experiment showed no difference when comparing 50 mg/day, 100 mg/day, or 200 mg/day versus 25 mg/day.

Sensitivity analyses

In our sensitivity analysis, only including studies with proper randomization, proper allocation concealment, and proper blinding yielded similar results with respect to mean changes in systolic and diastolic blood pressure, although the number of trials was small, so there may be important differences in treatment effects based on risk of bias. Therefore, we do not present any of these results, as they did not contribute to a difference in our conclusions. We did not impute any of the blood pressure standard deviations, so a sensitivity analysis for this domain was not necessary.

DISCUSSION

Summary of main results

There is insufficient evidence to draw any conclusions on the effects of eplerenone versus placebo for mortality, morbidity, or serious adverse events, as none of the included studies reported on any clinically meaningful outcomes.

Of the three studies that had adequate adverse event reporting, there were no differences in the incidence of participants experiencing any adverse event or adverse events leading to withdrawal in the eplerenone group compared to placebo (Figure 4). However, we could not analyze these results based on dose, and the potential harms related to increased daily doses of eplerenone are unknown.

Meta-analysis of the five parallel-group randomized controlled trials found a reduction in systolic blood pressure of 9.21 mmHg (95% CI −11.08 to −7.34; P < 0.001) and a reduction in diastolic blood pressure of 4.18 mmHg (95% CI −5.03 to −3.33; P < 0.001) (Figure 5; Figure 6). These results were statistically significant. There was no evidence of heterogeneity between the studies in changes in diastolic blood pressure. We found moderate heterogeneity between the studies in changes in systolic blood pressure. There may be a dose-response effect with eplerenone at a dose of 400 mg/day; however, this finding is based on a single study (Weinberger 2002). The confidence intervals around the mean end-of-study blood pressure for doses ranging from 50 mg/day to 200 mg/day all overlapped. Thus, it appears that doses of more than 50 mg/day do not produce further reductions in systolic or diastolic blood pressure.

Overall completeness and applicability of evidence

While we attempted to contact authors of all five included studies, we only obtained further study information for White 2003. Contact with authors of White 2003 did not yield further information on clinical outcomes of mortality, morbidity, or serious adverse events. However, we were able to obtain further detail on blinding, allocation concealment, and randomization to better assess the risk of bias in the study. There was an underreporting of adverse effects in two of the studies (Calhoun 2011; Saruta 2004), which did not report the number of participants who withdrew due to adverse events or the number of participants with at least one adverse event.

It is interesting to note that the baseline mean BP was 153/101 mmHg in the intervention group and 152/100 mmHg in the placebo group across the included studies. This level of BP corresponds to the categorization of mild hypertension. A previous review (Diao 2014) suggested that there is no clear evidence that treatment of mild hypertension leads to reductions in the risk of morbidity and mortality.

Quality of the evidence

The effect sizes for reducing blood pressure that we calculated could be overestimates based on the unclear blinding used in three of the five included studies. Inappropriate blinding of outcome assessors, study participants, or both could exaggerate the effects of eplerenone on blood pressure by over-reporting expected or desirable results. Only three included trials adequately reported on the number of participants who withdrew due to adverse events and the number of participants with at least one adverse event. Lastly, the reporting of adverse events was not stratified by dose. Therefore, we could not assess the harm due to eplerenone or based on its dose. This would be of particular interest to determine whether doses of eplerenone of 400 mg/day contributed to more significant harm.

Potential biases in the review process

Three independent review authors assessed the studies, and a fourth validated their judgement when any differences in interpretation arose. We undertook this process to screen 307 titles and abstracts as well as 78 full-text articles, and to extract data from the five included studies for qualitative and quantitative analysis. None of the authors in this review have any conflicts of interest to declare.

Agreements and disagreements with other studies or reviews

The authors of this review are aware of one published review assessing the use of monotherapy eplerenone for treating essential hypertension (Pelliccia 2014). That review found statistically significant decreases in systolic blood pressure of 8.1 mmHg (95% CI −8.2 to −8.0) and in diastolic blood pressure of 4.1 mmHg (95% CI −4.1 to −4.0 mmHg). These results are very similar; however, Pelliccia 2014 included Krum 2002, which compared eplerenone plus ACE inhibitor or an angiotensin receptor blocker combination versus placebo plus ACE inhibitor or an angiotensin receptor blocker combination; this was not eplerenone monotherapy, so we excluded it from our review.

In a meta-analysis of spironolactone versus placebo for hypertension, Batterink 2010 found that spironolactone lowered SBP by 20.09 mmHg and DBP by 6.75 mmHg. In a meta-analysis of ACE inhibitors versus placebo, maximal blood pressure lowering for the ACE inhibitor class of drugs was −7.68 mmHg (95% CI -8.45, -6.91) for SBP and −4.59 mmHg (95% CI −4.99, −4.19) for DBP (Heran 2009). Another review found that beta-blockers reduced systolic and diastolic blood pressure by approximately 11 mmHg and 6 mmHg, respectively, compared to placebo (Wiysonge 2017). Indirect evidence suggests that eplerenone lowers blood pressure to a lesser extent than spironolactone but to a similar extent as ACE inhibitors and beta-blockers.

AUTHORS' CONCLUSIONS

Implications for practice

Eplerenone 50 to 200 mg/day lowers blood pressure in people with primary hypertension by 9.21 mmHg systolic and 4.18 mmHg diastolic compared to placebo, with no difference of effect between doses of 50 mg/day to 200 mg/day. A dose of 25 mg/day did not produce a statistically significant reduction in systolic or diastolic blood pressure and there is insufficient evidence for doses above 200 mg/day. There is currently no available evidence to determine the effect of eplerenone on clinically meaningful outcomes such as all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, serious adverse events, fatal and non-fatal stroke, or fatal and non-fatal myocardial infarction in hypertensive patients. The evidence available on side effects is insufficient and of low quality, which makes it impossible to draw conclusions about potential harm associated with eplerenone treatment in hypertensive patients.

Implications for research

Although practitioners have used eplerenone for hypertension since 2002, studies have not yet shown a reduction in adverse cardiovascular events. Because the use of eplerenone in hypertension is generally limited to people already receiving other antihypertensive medications, further studies of eplerenone 50 mg/day to 100 mg/day as first-line, second-line, or third-line therapy are necessary. Additionally, studies with longer follow-up are necessary to allow for analysis of the effect of eplerenone on clinically meaningful outcomes such as mortality and morbidity.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Calhoun 2011

Methods	**Study design**: randomized controlled trial **Study grouping**: parallel group
Participants	**Baseline characteristics** Eplerenone 50 mg twice daily • *Female (%)*: 33.3 (28/84) • *Mean age (years ± SD)*: 55.3 (± 9.1 • *Black (%)*: 11.9 (10/84) • *White (%)*: 86.9 (73/84) • *Asian (%)*: 1.2 (1/84) • *SBP (mmHg, mean ± SD)*: 158.2 ± 10.9 • *DBP (mmHg, mean ± SD)*: 100.4 ± 3.6 • *24 h ASBP (mean ± SD)*: 143.1 ± 14.3 • *24 h ADBP (mean ± SD)*: 90.8 ± 9.4 • *Mean duration of hypertension (years)*: 8.1 • *eGFR (mL/min/1.73 m^2, mean ± SD)*: 84.2 ± 12.8 Placebo • *Female (%)*: 40.3 (31/77) • *Mean age (years ± SD)*: 53.9 ± 8.7 • *Black (%)*: 6.5 (5/77) • *White (%)*: 90.9 (70/77) • *Asian (%)*: 1.3 (1/77) • *SBP (mmHg, mean ± SD)*: 156.7 ± 10.1 • *DBP (mmHg, mean ± SD)*: 100.5 ± 3.8 • *24h ASBP (mean ± SD)*: 141.6 ± 12.5 • *24h ADBP (mean ± SD)*: 89.5 ± 10.4 • *Mean duration of hypertension (years)*: 5.3 • *eGFR (mL/min/1.73 m^2, mean ± SD)*: 85.4 ± 15.2 **Inclusion criteria**: • Between 18 and 75 years of age. Stage 1 to 2 hypertension, either untreated or treated with ≤ 2 antihypertensive agents • Seated diastolic BP (DBP) was ≥ 95 mmHg and < 110 mmHg after a 2-week screening/washout period followed by a 2-week placebo-controlled run-in period • Women were required to be postmenopausal for 1 year, to be surgically sterile, or to be using an effective method of birth control other than hormonal contraceptives **Exclusion criteria**: • History of severe hypertension (BP ≥ 180/110 mmHg) • A history of diabetes mellitus

Calhoun 2011 *(Continued)*

- A history of cardiovascular disease, including coronary artery disease, myocardial infarction, stroke, transient ischemic attack, any revascularization procedure, congestive heart failure, or hemodynamically significant carotid or peripheral arterial disease
- An estimated glomerular filtration rate < 60 mL/min/1.73 m^2
- A serum potassium > 5.2 mEq/L or < 3.5 mEq/L
- Use of medications likely to affect BP, including nonsteroidal anti-inflammatory drugs; or use of glucocorticoids, potent CYP3A4 inhibitors, or potassium supplements

Pretreatment: eplerenone group had a higher mean duration of hypertension

Interventions	**Intervention characteristics** Placebo Eplerenone 50 mg twice daily
Outcomes	*Blood pressure (seated)* • **Outcome type**: continuous outcome *Mean sitting clinic SBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline *Mean sitting clinic DBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in 24h mean DBP* • **Outcome type**: continuous outcome • **Reporting**: partially reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in 24h mean SBP* • **Outcome type**: continuous outcome • **Reporting**: partially reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline
Identification	**Sponsorship source**: Novartis Pharma AG (Switzerland) **Country**: Argentina, Australia, France, Germany, the Netherlands, Romania, Spain, Sweden, and the USA **Setting**: Clinics/physician's offices in Argentina, Australia, France, Germany, the Netherlands, Romania, Spain, Sweden, and the USA

Calhoun 2011 *(Continued)*

Comments: patients recruited between 11 September 2008 and 6 April 2009; treatment continued until 2 July 2009

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Notes —

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Quote: "Randomization sequences were generated by the interactive voice-response system provider." Quote: "A validated system automated the random assignment of patient numbers to randomization numbers, which were linked to the different treatment groups and the medication numbers on treatment packs." Quote: "interactive voice-response system was used to randomly assign patients to 1 of 6 treatment groups"
Allocation concealment	Low risk	Quote: "A validated system automated the random assignment of patient numbers to randomization numbers, which were linked to the different treatment groups and the medication numbers on treatment packs." Quote: "The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, appearance, taste, and odor."
Blinding of participants and personnel All outcomes	Low risk	Quote: "Patients, investigators, people performing the assessments, and data analysts remained blinded to treatment assignments from the time of randomization until database lock. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, appear- ance, taste, and odor." Quote: "Both patients and investigators were blinded to the treatment assigned at randomization."
Blinding of outcome assessors All outcomes	Low risk	Quote: "Patients, investigators, people performing the assessments, and data analysts remained blinded to treatment assignments from the time of randomization until database lock."
Incomplete outcome data All outcomes	Unclear risk	Quote: "Of the randomised patients, 522 had post baseline BP measurements, and 474 completed the 8-week double-blind period . . .The proportion of patients who discontinued during the double-blind treatment period was higher in the placebo group (13.0%, 10 of 77) compared with the 5 active treatment groups (values ranged from 6.8% [6 of 88] in the 0.5-mg once-daily LCI699 group to 10.7% [9/84] in the 50-mg twice-daily eplerenone group), primarily because of a lack of efficacy as judged by the investigator." Judgement comment: percentage of withdrawals from groups ranges from 6.8% to 13.0%. Not enough information to assess the risk of bias from missing data.

Calhoun 2011 *(Continued)*

Selective outcome reporting	Low risk	Quote: "The primary end point for this trial was mean sitting DBP. Secondary end points included mean sitting systolic BP and 24-hour ambulatory DBP and SBP." Judgement comment: all outcomes specified in registered clinicaltrials.gov protocol were reported.
Other sources of bias	High risk	Quote: "This support was funded by Novartis." Quote: "This study was designed collaboratively by the academic authors and the sponsor, Novartis Pharma AG (Switzerland). The sponsor was responsible for collecting data from investigational sites to create the clinical database and for the data analysis." Quote: "None of the authors received compensation for the evaluation, writing, or editing of this article. Dr Calhoun has received consulting fees, honoraria, and research funding from Novartis. Dr White has received consulting fees for safety committee work with aliskiren, and research funding from Novartis has been granted to his university; in addition, Dr White was reimbursed by Novartis for travel/accommodation to present this study at the American College of Cardiology in Atlanta in 2010. Dr Krum has received a research grant from Novartis. Dr Me ´ nard has received consulting fees from Novartis, Roche, and Actelion and is a member of the scientific council of Actelion. Drs Guo, Bermann, Lefkowitz, and Trapani are employees of Novartis."

Flack 2003

Methods	**Study design**: randomized controlled trial **Study grouping**: parallel group
Participants	**Baseline characteristics** Eplerenone 50 mg daily • *Female (%)*: 64.3 (117/182) • *Age (years, mean ±SD)*: 50.9 ± 11.2 • *Black (%)*: 63.2 (115/182) • *Weight female (kg, mean ±SD)*: 86.5 ± 18.5 • *Weight male (kg, mean ±SD)*: 92.7 ± 17.4 • *Seated SBP (mmHg, mean ±SD)*: 149.3 ± 11.3 • *Seated DBP (mmHg, mean ±SD)*: 98.9 ± 3.5 • *HR (beats/min, mean ±SD)*: 73.6 ± 8.3 • *UA/CR (ug/mmol)*: 941 • *Active renin (mU/L)*: 11.3 • *Serum aldosterone (ng/dL)*: 7.0 Placebo • *Female (%)*: 53.6 (97/181) • *Age (years, mean ±SD)*: 52.1 ± 11.1 • *Black (%)*: 62.4 (113/181) • *Weight female (kg, mean ±SD)*: 83.9 ± 18.9 • *Weight male (kg, mean ±SD)*: 93.2 ± 16.9 • *Seated SBP (mmHg, mean ±SD)*: 148.9 ± 11.6 • *Seated DBP (mmHg, mean ±SD)*: 99.1 ± 3.6

Flack 2003 *(Continued)*

- *HR (beats/min, mean ±SD)*: 73.1 ± 8.9
- *UA/CR (ug/mmol)*: 991
- *Active renin (mU/L)*: 12.0
- *Serum aldosterone (ng/dL)*: 7.5

Inclusion criteria:

- Men and women ≥ 18 years old
- Mild-to-moderate hypertension (SBP < 180 mmHg and DBP 95-109 mmHg without medication)
- Self-identified as black or white
- Patients on 1 or 2 antihypertensives and BP < 140/90

Exclusion criteria:

- Patients with known secondary hypertension, insulin-dependent diabetes, hepatic disease, elevated serum creatinine levels, evidence of alcohol/drug abuse, unable to be withdrawn from antihypertensives, regularly used corticosteroids, class II to IV heart failure, myocardial infarction, coronary revascularization, stroke or transient ischemic attack within past 6 months, current unstable angina, or any serious medical condition (not described)
- History of NYHA II-IV congestive heart failure
- Myocardial infarction, coronary revascularization, stroke, or TIA within the past 6 months
- Current unstable angina
- Any serious medical condition

Pretreatment: missing baseline data for serum aldosterone in N = 61 (placebo); missing baseline UA/CR for N = 63 (placebo) and N = 50 (eplerenone); missing baseline RAAS profile in N = 60 (placebo) and N = 45 (eplerenone). They report no significant differences between the three groups, but higher % female in eplerenone group (64.3% vs 53.6%)

Interventions

Intervention characteristics

Eplerenone 50 mg daily

Placebo

Outcomes

Mean change in SBP

- **Outcome type**: continuous outcome
- **Reporting**: fully reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Mean change in DBP

- **Outcome type**: continuous outcome
- **Reporting**: fully reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Any adverse event

- **Outcome type**: adverse event
- **Reporting**: fully reported
- **Direction**: lower is better
- **Data value**: endpoint

Adverse event leading to discontinuation

Flack 2003 *(Continued)*

- **Outcome type**: adverse event
- **Direction**: lower is better
- **Data value**: endpoint

Identification	**Sponsorship source**: Pharmacia Corporation, Skokie Illinois **Country**: South Africa and USA **Setting**: 8 centers in South Africa, 41 centers in USA **Comments**: 4 January 2000 to 19 January 2001 **Author's name**: John M Flack **Institution**: Department of Internal Medicine, Wayne State University, Detroit, Michigan **Email**: JFlack@intmed.wayne.edu **Address**: 4201 St. Antoine, Suite 2EDetroit, Michigan 48201
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence Generation	Unclear risk	Judgement comment: method of sequence generation not described
Allocation concealment	Unclear risk	Judgement comment: method of allocation concealment not described
Blinding of participants and personnel All outcomes	Unclear risk	Quote: "double-blind" Judgement comment: not described how blinding was achieved or which participants were blinded
Blinding of outcome assessors All outcomes	Unclear risk	Judgement comment: blinding of outcome assessors not described
Incomplete outcome data All outcomes	High risk	Quote: "A total of 551 patients were randomized to study treatment, and 352 completed 16 weeks of treatment. Of these, 16 patients (4 placebo, 8 eplerenone, and 4 losartan) had no post-baseline assessment; therefore, 535 patients were included in the cohort for efficacy analysis (Table 1)." Judgement comment: 16 patients had no post baseline assessment and were not included in the efficacy analysis. Blood pressure data from these 16 patients was not known.
Selective outcome reporting	Unclear risk	Quote: "The primary study end point was the mean change in DBP from baseline to the final visit. Secondary end points were the mean change from baseline to the final visit for SBP and DBP within and between racial groups; improvement in urinary protein excretion as measured by changes in the urinary albumin/creatinine ratio (UA/CR); and the effect of eplerenone in selected subpopulations, including women, obese patients, patients with SBP 160 mm Hg, elderly patients, and patients with microalbuminuria. Exploratory analyses assessed the rate of response to therapy and the relationships between BP changes and baseline active renin or aldosterone levels." Judgement comment: all primary study outcomes specified appear to have been reported. Secondary end points of improvement in urinary protein excretion as measured by changes in the urinary albumin/creatinine ratio and the

Flack 2003 *(Continued)*

		effect of eplerenone in obese patients, elderly patients, and patients with microalbuminuria were not reported.
Other sources of bias	Unclear risk	Judgement comment: funding source unknown

Saruta 2004

Methods	**Study design**: randomized controlled trial **Study grouping**: parallel group
Participants	**Baseline characteristics** Eplerenone 50 mg daily • *Female (%)*: 36.7 (18/49) • *Mean age (years ±SD)*: 54.2 ± 11.3 • *Mean active renin (mU/L)*: 5.7 (N = 48) • *Asian (%)*: 100 (49/49) • *BMI female (mean kg/m^2 ±SD)*: 24.1 ± 2.6 • *BMI male (mean kg/m^2 ±SD)*: 25.6 ± 2.9 • *Mean SBP (mmHg ±SD)*: 153.5 ± 13.34 • *Mean DBP (mmHg ±SD)*: 100.2 ± 4.59 • *24-h ABPM: SBP (mmHg ±SD)*: 150.0 ± 13.76 (N = 15) • *24-h ABPM: DBP (mmHg ±SD)*: 92.6 ± 5.16 (N = 15) Placebo • *Female (%)*: 32.0 (16/50) • *Mean age (years ±SD)*: 54.3 ± 10.55 • *Mean active renin (mU/L)*: 10.1 (N = 48) • *Asian (%)*: 100 (50/50) • *BMI female (mean kg/m^2 ±SD)*: 23.3 ± 3.5 • *BMI male (mean kg/m^2 ±SD)*: 25.8 ± 3.3 • *Mean SBP (mean mmHg ±SD)*: 150.5 ± 11.67 • *Mean DBP (mean mmHg ±SD)*: 100.6 ± 5.64 • *24-hour ABPM: SBP (mmHg ±SD)*: 152.4 ± 15.92 (N = 13) • *24-hour ABPM: DBP (mmHg ±SD)*: 96.1 ± 6.51 (N = 13) Eplerenone 100 mg daily • *Female (%)*: 30.4 (14/46) • *Mean age (years ±SD)*: 52.8 ± 10.02 • *Mean active renin (mU/L)*: 6.3 (N =) • *Asian (%)*: 100 (46/46) • *BMI female (mean kg/m^2 ±SD)*: 23.0±3.4 • *BMI male (mean kg/m^2 ±SD)*: 25.0±3.3 • *Mean SBP (mean mmHg ±SD)*: 156.1±14.25 • *Mean DBP (mean mmHg ±SD)*: 101.7±5.72 • *24-hour ABPM: SBP (mean mmHg ±SD)*: 153.1±14.21 (N=14) • *24-hour ABPM: DBP (mean mmHg ±SD)*: 96.4±7.77 (N=14) Eplerenone 200 mg daily

Saruta 2004 *(Continued)*

- *Female (%)*: 27.1 (13/48)
- *Mean age (years ±SD)*: 52.6 ± 10.76
- *Mean active renin (mU/L)*: 8.0 (N = 47)
- *Asian (%)*: 100 (48/48)
- *BMI female (mean kg/m^2 ±SD)*: 25.0 ± 3.3
- *BMI male (mean kg/m^2 ±SD)*: 25.1 ± 2.4
- *Mean SBP (mean mmHg ±SD)*: 152.8 ± 16.10
- *Mean DBP (mean mmHg ±SD)*: 100.9 ± 5.05
- *24-hour ABPM: SBP (mean mmHg ±SD)*: 155.1 ± 13.49 (N = 16)
- *24-hour ABPM: DBP (mean mmHg ±SD)*: 97.3 ± 6.34 (N = 16)

Inclusion criteria:

- Men and women aged 20-80 years old
- History of hypertension (treated or untreated)
- Untreated hypertension as defined by a cuff seated diastolic BP (seDBP) ≥ 95 mmHg and < 115 mmHg
- Postmenopausal or surgically sterile women
- ECG without evidence of an arrhythmia requiring treatment
- A serum potassium level of 3.55. mmol/L

Exclusion criteria:

- Secondary, severe, labile, or malignant hypertension
- New York Heart Association class II–IV heart failure
- Coronary artery disease
- Severe valvular heart disease
- Cerebrovascular disease
- Diabetes mellitus
- Liver disease
- Kidney disease
- Taking systemic vasodilators/vasoconstrictors, alfa- or beta-blockers for treatment of prostatic hypertrophy, other drugs known to affect BP, antiarrhythmics, systemic glucocorticoids, hormonal replacement, immunosuppressive or cytotoxic drugs, nicotine, fluconazole, itraconazole, erythromycin, or regular use of NSAIDs
- Taking medications that could alter the GI absorption of study medication. History of alcohol or substance abuse. Allergy or sensitivity to study drug

Interventions	**Intervention characteristics** Eplerenone 50 mg daily Placebo Eplerenone 100 mg daily Eplerenone 200 mg daily
Outcomes	*Blood pressure (seated)* • **Outcome type**: continuous outcome *Pulse pressure (change from baseline)* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline

Saruta 2004 *(Continued)*

- **Notes**: pulse pressure = SBP - DBP

Mean change in SBP

- **Outcome type**: continuous outcome
- **Reporting**: partially reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Mean change in DBP

- **Outcome type**: continuous outcome
- **Reporting**: partially reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Mean change in 24 h ambulatory SBP

- **Outcome type**: continuous outcome
- **Reporting**: partially reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Mean change in 24 h ambulatory DBP

- **Outcome type**: continuous outcome
- **Reporting**: partially reported
- **Unit of measure**: mmHg
- **Direction**: lower is better
- **Data value**: change from baseline

Identification	**Sponsorship source**: Grant from Pfizer Inc **Country**: Japan **Setting**: 22 centers in Japan **Comments**: **Author's name**: Takao Saruta **Institution**: Department of Internal Medicine, Keio University School of Medicine **Email**: takao_saruta@ybb.ne.jp or saruta@sc.itc.keio.ac.jp **Address**: 35 Shinanomachi, Shinjuku-ku Tokyo 160-8582, Japan
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence Generation	Unclear risk	Judgement comment: No information provided. An email was sent to both takao_saruta@ybb.ne.jp and saruta@sc.itc.keio.ac.jp on 14 November 2015 for clarification.

Saruta 2004 *(Continued)*

Allocation concealment	Unclear risk	Judgement comment: not reported
Blinding of participants and personnel All outcomes	Unclear risk	Judgement comment: the study did not specify how blinding of participants or personnel was done.
Blinding of outcome assessors All outcomes	Unclear risk	Judgement comment: study did not address this. An email has been sent to both takao_saruta@ybb.ne.jp and saruta@sc.itc.keio.ac.jp on 14 November2015 for clarification.
Incomplete outcome data All outcomes	Low risk	Quote: "one patient in the eplerenone 50-mg group had no post dose BP measurement due to withdrawal of informed consent and was therefore excluded from the efficacy analysis." Judgement comment: only 1 patient dropped out. No other missing data for adjusted mean change in systolic and diastolic blood pressure at week 8. Unlikely to affect results in the group of 49.
Selective outcome reporting	Low risk	Judgement comment: the study protocol is not available but published report included all of the prespecified outcomes
Other sources of bias	High risk	Quote: "Disclosure: This research was supported by a grant from Pfizer Inc."

Weinberger 2002

Methods	**Study design**: randomized controlled trial **Study grouping**: parallel group
Participants	**Baseline characteristics** Eplerenone 50 mg daily • *Female (%)*: 30 • *White (%)*: 67 • *African American (%)*: 19 • *Hispanic (%)*: 15 • *Asian/other (%)*: 0 • *Seated SBP (mmHg, mean ±SD)*: 155.6 • *Seated DBP (mmHg, mean ±SD)*: 100.8 • *HR (beats/min, mean ±SD)*: 75.7 • *Standing SBP (mmHg, mean)*: 154.7 • *Standing DBP (mmHg, mean)*: 101.6 Placebo • *Female (%)*: 4 • *White (%)*: 58 • *African American (%)*: 25 • *Hispanic (%)*: 17 • *Asian/other (%)*: 0 • *Seated SBP (mmHg, mean ±SD)*: 153.5 • *Seated DBP (mmHg, mean ±SD)*: 101.3 • *HR (beats/min, mean ±SD)*: 76.3 • *Standing SBP (mmHg, mean)*: 153.1

Weinberger 2002 *(Continued)*

- *Standing DBP (mmHg, mean)*: 102.9

Eplerenone 100 mg daily

- *Female (%)*: 39
- *White (%)*: 67
- *African American (%)*: 24
- *Hispanic (%)*: 8
- *Asian/other (%)*: 0
- *Seated SBP (mmHg, mean ±SD)*: 153.0
- *Seated DBP (mmHg, mean ±SD)*: 100.8
- *HR (beats/min, mean ±SD)*: 74.5
- *Standing SBP (mmHg, mean)*: 153.8
- *Standing DBP (mmHg, mean)*: 102.1

Eplerenone 400 mg daily

- *Female (%)*: 36
- *White (%)*: 66
- *African American (%)*: 25
- *Hispanic (%)*: 5
- *Asian/other (%)*: 4
- *Seated SBP (mmHg, mean ±SD)*: 152.2
- *Seated DBP (mmHg, mean ±SD)*: 101.7
- *HR (beats/min, mean ±SD)*: 73.7
- *Standing SBP (mmHg, mean)*: 151.2
- *Standing DBP (mmHg, mean)*: 102.5

Eplerenone 25 mg twice daily

- *Female (%)*: 27
- *White (%)*: 75
- *African American (%)*: 15
- *Hispanic (%)*: 9
- *Asian/other (%)*: 2
- *Seated SBP (mmHg, mean ±SD)*: 155.7
- *Seated DBP (mmHg, mean ±SD)*: 101.0
- *HR (beats/min, mean ±SD)*: 75.0
- *Standing SBP (mmHg, mean)*: 154.7
- *Standing DBP (mmHg, mean)*: 101.9

Eplerenone 50 mg twice daily

- *Female (%)*: 30
- *White (%)*: 70
- *African American (%)*: 19
- *Hispanic (%)*: 9
- *Asian/other (%)*: 2
- *Seated SBP (mmHg, mean ±SD)*: 153.6
- *Seated DBP (mmHg, mean ±SD)*: 101.2
- *HR (beats/min, mean ±SD)*: 74.0
- *Standing SBP (mmHg, mean)*: 153.4
- *Standing DBP (mmHg, mean)*: 102.1

Eplerenone 200 mg twice daily

Weinberger 2002 *(Continued)*

- *Female (%)*: 31
- *White (%)*: 73
- *African American (%)*: 15
- *Hispanic (%)*: 10
- *Asian/other (%)*: 2
- *Seated SBP (mmHg, mean ±SD)*: 155.4
- *Seated DBP (mmHg, mean ±SD)*: 102.0
- *HR (beats/min, mean ±SD)*: 73.4
- *Male (%)*: 69
- *Standing SBP (mmHg, mean)*: 154.7
- *Standing DBP (mmHg, mean)*: 103.0

Inclusion criteria:

- 21-80 years old with both seated, cuff-assessed diastolic blood pressure (DBP) ≥ 95 mmHg and < 114 mmHg and a 24-h mean DBP ≥ 85 mmHg determined by a 24-h ambulatory BP monitoring (ABPM) device
- Medication compliance (80%) during the single-blind placebo lead-in period was required to qualify for randomization

Exclusion criteria:

- Secondary, severe, or malignant hypertension with or without retinopathy
- Regular use of systemic medications known to influence BP
- Regular use of nonsteroidal antiinflammatory drugs
- Myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, angina pectoris, or intermittent claudication within the previous 6 months
- Severe aortic or mitral valvular disease and cardiac arrhythmia requiring medical treatment or causing haemodynamically relevant disturbances
- Hypertrophic cardiomyopathy or congestive heart failure requiring digoxin or diuretic therapy
- Stroke or transient ischemic attack within the previous 6 months
- Insulin-dependent diabetes mellitus
- Acute or chronic hepatic disease
- Serum creatinine > 1.5 mg/dL or serum potassium > 5.0 mEq/L
- History of alcohol or drug abuse
- Known hypersensitivity to spironolactone or steroids
- Use of any other investigational medication 30 days before this study
- Night-shift employment
- Upper arm circumference > 42 cm

Pretreatment: study notes no differences in baseline characteristics between groups. Groups look well-balanced

Interventions	**Intervention characteristics** Eplerenone 50 mg daily Placebo Eplerenone 100 mg daily Eplerenone 400 mg daily Eplerenone 25 mg twice daily Eplerenone 50 mg twice daily Eplerenone 200 mg twice daily

Weinberger 2002 *(Continued)*

Outcomes	*Change from baseline in SBP (seated)* • **Outcome type**: continuous outcome *Change from baseline in DBP (seated)* • **Outcome type**: continuous outcome *Change from baseline in 24 h ambulatory BP monitoring (SBP)* • **Outcome type**: continuous outcome • **Reporting**: partially reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in 24 h ambulatory BP monitoring (DBP)* • **Outcome type**: continuous outcome • **Reporting**: partially reported • **Unit of measure**: mmHg • **Direction**: lower is better • **Data value**: change from baseline *Number of patients with any adverse events (occurring in at least 5% of patients)* • **Outcome type**: adverse event • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: endpoint *Number of patients discontinued medication due to AE* • **Outcome type**: adverse event • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: endpoint
Identification	**Sponsorship source**: Pharmacia Corporation, Skokie IL **Country**: 48 US sites **Author's name**: Myron H Weinberger **Institution**: Indiana University School of Medicine, Hypertension Research Center **Email**: mweinbe@iupui.edu **Address**: 541 Clinical Drive #423Indianapolis, IN46202-5111
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Quote: "Qualified patients in the double-blind treatment period were randomised by a computer-generated schedule to 50, 100, or 400 mg of eplerenone administered once daily or in divided doses; 50 mg of spironolactone twice daily; or placebo."

Weinberger 2002 *(Continued)*

Allocation concealment	Low risk	Judgement comment: allocation of all patients simultaneously after run-in via computer randomization.
Blinding of participants and personnel All outcomes	Unclear risk	Quote: "8-week double-blind treatment period." Judgement comment: unclear, because exactly who was blinded is not known. No mention of matching placebo used to mimic twice daily dosing of eplerenone groups
Blinding of outcome assessors All outcomes	Unclear risk	Judgement comment: no reference to blinding of assessors made. No mention of double dummy design.
Incomplete outcome data All outcomes	Unclear risk	Quote: "Overall, 417 patients were randomised to receive at least one dose of study medication and were subsequently included in the safety analyses. Of these, 409 had at least one evaluation after their baseline evaluation and were included in the efficacy analyses. Five patients were excluded because of protocol noncompliance and three were lost to follow-up. An additional 39 patients did not complete the study because of treatment failure (7), loss to follow-up (2), protocol noncompliance (16), pre-existing protocol violation (3), or adverse events (11)." Judgement comment: not clear how 11.3% patient withdrawals were distributed across groups or how missing data was dealt with.
Selective outcome reporting	Unclear risk	Judgement comment: no protocol available.
Other sources of bias	High risk	Quote: "This study was supported by Pharmacia Corporation, Skokie, IL."

White 2003

Methods	**Study design**: randomized controlled trial **Study grouping**: parallel group
Participants	**Baseline characteristics** Eplerenone 50 mg daily • *Female (%)*: 48/87 (55) • *Age (years)*: 54 ± 9 • *Black (%)*: 18/87 (21%) • *Seated SBP (mmHg, mean ±SD)*: 154 ± 12 • *Seated DBP (mmHg, mean ±SD)*: 100 ±5 • *BMI female (mean kg/m^2 ±SD)*: 30 ± 6 • *BMI male (mean kg/m^2 ±SD)*: 30 ± 6 • *24-h SBP (mmHg, mean ±SD)*: 149 ± 12 • *24-h DBP (mmHg, mean ±SD)*: 95 ± 7 Placebo • *Female (%)*: 54/90 (60) • *Age (years)*: 54 ± 11 • *Black (%)*: 20/90 (22%) • *Seated SBP (mmHg, mean ±SD)*: 151 ± 11

White 2003 *(Continued)*

- *Seated DBP (mmHg, mean ±SD)*: 100 ± 4
- *BMI female (mean kg/m^2 ±SD)*: 30 ± 5
- *BMI male (mean kg/m^2 ±SD)*: 29 ± 4
- *24-h SBP (mmHg, mean ±SD)*: 147 ± 10
- *24-h DBP (mmHg, mean ±SD)*: 94 ± 6

Eplerenone 25 mg daily

- *Female (%)*: 27/45
- *Age (years)*: 51 ± 11
- *Black (%)*: 11/45 (24%)
- *Seated SBP (mmHg, mean ±SD)*: 151 ±13
- *Seated DBP (mmHg, mean ±SD)*: 100 ± 4
- *BMI female (mean kg/m^2 ±SD)*: 32 ± 5
- *BMI male (mean kg/m^2 ±SD)*: 29 ± 4
- *24-h SBP (mmHg, mean ±SD)*: 146 ± 12
- *24-h DBP (mmHg, mean ±SD)*: 95 ± 6

Eplerenone 100 mg daily

- *Female (%)*: 47/90
- *Age (years)*: 52 ± 10
- *Black (%)*: 17/90 (19%)
- *Seated SBP (mmHg, mean ±SD)*: 154 ± 12
- *Seated DBP (mmHg, mean ±SD)*: 100 ± 5
- *BMI female (mean kg/m^2 ±SD)*: 29 ± 5
- *BMI male (mean kg/m^2 ±SD)*: 30 ± 5
- *24-h SBP (mmHg, mean ±SD)*: 150 ± 11
- *24-h DBP (mmHg, mean ±SD)*: 96 ± 7

Eplerenone 200 mg daily

- *Female (%)*: 48/88
- *Age (years)*: 53 ± 11
- *Black (%)*: 19/88 (22%)
- *BMI female (mean kg/m^2 ±SD)*: 30 ± 4
- *BMI male (mean kg/m^2 ±SD)*: 29 ± 6
- *24-h SBP (mmHg, mean ±SD)*: 153 ± 12
- *24-h DBP (mmHg, mean ±SD)*: 96 ± 8

Inclusion criteria: adult men and women were included if they had untreated hypertension, their seated clinic systolic BPs were < 180 mmHg, the clinic diastolic BP was 95-110 mmHg, and the 24-hour mean diastolic BP was ≥ 85 mm Hg.

Exclusion criteria: participant were excluded from the trial if they had recent myocardial infarction or unstable angina, congestive heart failure, clinically significant liver or renal disease, known secondary hypertension, or uncontrolled diabetes mellitus (glycohaemoglobin > 10%). Men and women whose serum creatinine was > 1.5 mmol/L or > 1.3 mmol/L, respectively, or whose serum potassium was > 5.0 mmol/L at baseline were also excluded from the trial.

Pretreatment: no significant group differences.

Interventions	**Intervention characteristics** Eplerenone 50 mg daily Placebo

White 2003 *(Continued)*

	Eplerenone 25 mg daily Eplerenone 100 mg daily Eplerenone 200 mg daily
Outcomes	*Change in SBP (seated)* • **Outcome type**: continuous outcome • **Direction**: lower is better • **Data value**: change from baseline *Change in DBP (seated)* • **Outcome type**: continuous outcome • **Direction**: lower is better • **Data value**: change from baseline *Change in 24 h ambulatory SBP* • **Outcome type**: continuous outcome • **Direction**: lower is better • **Data value**: change from baseline *Change in 24 h ambulatory DBP* • **Outcome type**: continuous outcome • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in daytime SBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in daytime DBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in nighttime SBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: change from baseline *Change from baseline in nighttime DBP* • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Direction**: lower is better • **Data value**: change from baseline
Identification	**Sponsorship source**: **Country**: USA, Brazil

White 2003 *(Continued)*

Setting: Investigation sites, offices, clinics

Author's name: William B White

Institution: Section of Hypertension and Clinical Pharmacology, University of Connecticut School of Medicine, Farmington, Connecticut, USA

Email: wwhite@nso1.uchc.edu

Address: University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, Connecticut 06030-3940, USA

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence Generation	Unclear risk	Judgement comment: email response was unclear as to how sequence was generated as it was done by the sponsor Pharmacia, which no longer exists.
Allocation concealment	Low risk	Quote: "The study was a multicenter, double- blind, randomised, placebo-controlled, parallel arm trial." Judgement comment: allocation concealment was done via "bottles of unidentified investigational product", which was distributed from a central coordination site by the sponsor via an interactive voice response system to the study coordinator as per email response from Dr White.
Blinding of participants and personnel All outcomes	Low risk	Judgement comment: as per email response, "both study patients and site staff were blinded to treatment assignment - the study medication was in bottles of unidentified investigational product. The study coordinator used an IVRS process to obtain which bottles to use."
Blinding of outcome assessors All outcomes	Low risk	Judgement comment: as per email response, "the medication bottles are sent from a central location and are blinded. The outcome assessors had absolutely no way of knowing the randomization medication/code."
Incomplete outcome data All outcomes	Unclear risk	Quote: "There were 400 patients randomised into the 5 treatment arms by 47 investigative sites in the United States and Brazil with similar demographics and baseline clinic and ambulatory BP values . . . The percentage of patients withdrawn from the study was 22% in the placebo group, 27% in the eplerenone 25-mg group, 21% in the eplerenone 50-mg group, 11% in the eplerenone 100-mg group, and 14% in the eplerenone 200-mg group. The main reason for withdrawal after randomization was due to treatment failure: 12%, 9%, 7%, 1%, and 6% in the placebo, and eplerenone 25-, 50-, 100-, and 200-mg groups, respectively. Other reasons included lost to follow-up, protocol violations, noncompliance, adverse events, or patient withdrawal of consent." Judgement comment: unclear reasons for withdrawals in each group and how missing data was accounted for in the blood pressure outcomes.
Selective outcome reporting	Unclear risk	Judgement comment: per email response by Dr White, he is unable to "find a study protocol at this late date and there is no way for [him] to retrieve that since no one associated with the sponsor works for any manufacturer of eplerenone."
Other sources of bias	High risk	Judgement comment: research was sponsored by Pharmacia Corporation as per Dr White's email response.

ADBP: ambulatory diastolic blood pressure; **AE**: adverse event; **ASBP**: ambulatory systolic blood pressure; **BMI**: body mass index; **CYP3A4**: cytochrome P450 3A4;**DBP**: diastolic blood pressure; **ECG**: electrocardiogram; **eGFR**: estimated glomerular filtration rate; **GI**: gastrointestinal; **NSAID**: nonsteroidal anti-inflammatory drug; **NYHA**: New York Hear Association; **SBP**: systolic blood pressure; **SD**: standard deviation; **UA/CR**: urine albumin-to-creatinine ratio.

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

Study	Reason for exclusion
Amar 2013	Wrong intervention
Ando 2010	Wrong outcomes
Ando 2014a	Wrong intervention
Ando 2014b	Wrong intervention
Basile 2009	Wrong study design
Blanchard 2015	Wrong patient population
Burger 2005	Wrong study design
Burgess 2003	Wrong study design
Calhoun 2008	Wrong comparator
CCOHTA 2003	Wrong study design
Chaturvedi 2014	Wrong patient population
Christou 2011	Wrong outcomes
Christou 2012	Wrong outcomes
Cleland 2007	Wrong study design
Collier 2013	Wrong patient population
Conti 2003	Wrong study design
Dahal 2015	Studies involved resistant hypertension patients on multiple antihypertensives
Davis 2003	Wrong study design
Derer 2010	Wrong study design
Deswal 2010	Wrong patient population
Deswal 2011	Wrong patient population
Dieterich 2005	Wrong study design
Dobrucki 2003	Wrong study design
Epstein 1998	Wrong study design

Study	Reason for exclusion
Epstein 2002	Wrong comparator
Eschalier 2013	Wrong patient population
Flammer 2013	Wrong patient population
Funder 2005	Wrong study design
Funder 2010	Wrong study design
Hameedi 2000	Wrong study design
Hollenberg 2003	Wrong comparator
Hollenberg 2004	Wrong study design
Hwang 2011	Wrong outcomes
Hwang 2013	Wrong patient population
Jansen 2008	Wrong intervention
Joffe 2007	Wrong comparator
Karagiannis 2009	Wrong study design
Karns 2013	Wrong patient population
Krum 2002	Wrong intervention
Levy 2004	Wrong outcomes
Li 2010	Wrong patient population
Magill 2003	Wrong study design
Magni 2005	Wrong study design
Mantero 2000	Wrong study design
Montalescot 2014	Wrong patient population
NCT00147589	Wrong patient population
NCT00147615	Wrong patient population
NCT00649311	Wrong comparator
NCT00758524	Wrong study design
NCT00817635	Wrong intervention
NCT00825188	Wrong comparator
NCT00980031	Wrong patient population

Study	Reason for exclusion
NCT01275352	Wrong intervention
NCT01373086	No usable information obtained from responsible parties of terminated study
NCT02345044	Study protocol
Pelliccia 2014	Wrong study design
Pelliccia 2015	Review did not identify any new studies compared to our search
Pitt 2004	Wrong comparator
Romero 2011	Wrong study design
Roush 2016	Review did not identify any new studies compared to our search
Schmidt 2009	Wrong intervention
Stier 2003	Wrong study design
Struthers 2008	Wrong study design
Stults 2006	Wrong study design
Tomaschitz 2012	Wrong patient population
Toto 2010	Wrong study design
Trial 015 1999	No usable information obtained from responsible parties of unpublished study
Van Zwieten 2001	Wrong study design
Weber 2002	Wrong study design
Wenger 2008	Wrong study design
White 2010	Duplicate study
Yoo 2011	Wrong patient population

DATA AND ANALYSES

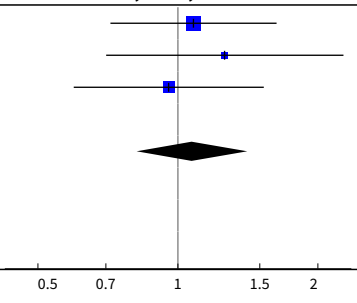
Comparison 1. Eplerenone monotherapy vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	3	1121	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.41]
2 Adverse event leading to withdrawal	3	1132	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.47, 2.55]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Systolic blood pres-sure	5	1437	Mean Difference (IV, Random, 95% CI)	-9.21 [-11.08, -7.34]
3.1 25 mg/day	1	66	Mean Difference (IV, Random, 95% CI)	-5.7 [-11.89, 0.49]
3.2 50 mg/day	4	645	Mean Difference (IV, Random, 95% CI)	-7.40 [-9.59, -5.22]
3.3 100 mg/day	4	433	Mean Difference (IV, Random, 95% CI)	-10.21 [-12.37, -8.05]
3.4 200 mg/day	2	172	Mean Difference (IV, Random, 95% CI)	-8.59 [-11.57, -5.62]
3.5 400 mg/day	1	121	Mean Difference (IV, Random, 95% CI)	-16.51 [-20.23, -12.78]
4 Diastolic blood pres-sure	5	1437	Mean Difference (IV, Fixed, 95% CI)	-4.18 [-5.03, -3.33]
4.1 25 mg/day	1	66	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.75, 1.75]
4.2 50 mg/day	4	645	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-4.98, -2.48]
4.3 100 mg/day	4	433	Mean Difference (IV, Fixed, 95% CI)	-4.64 [-6.18, -3.10]
4.4 200 mg/day	2	172	Mean Difference (IV, Fixed, 95% CI)	-4.13 [-6.44, -1.83]
4.5 400 mg/day	1	121	Mean Difference (IV, Fixed, 95% CI)	-7.69 [-11.42, -3.97]

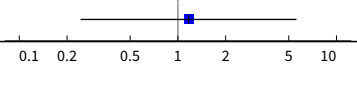
Analysis 1.1. Comparison 1 Eplerenone monotherapy vs placebo, Outcome 1 Any adverse event.

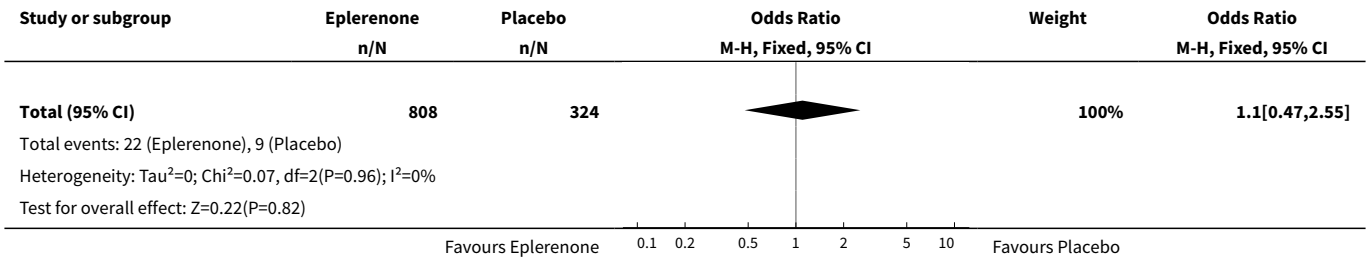
Study or subgroup	Eplerenone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Flack 2003	89/182	85/181		43.94%	1.08[0.72,1.63]
Weinberger 2002	150/305	23/53		20.1%	1.26[0.7,2.27]
White 2003	148/310	44/90		35.96%	0.96[0.6,1.53]
Total (95% CI)	**797**	**324**		**100%**	**1.07[0.82,1.41]**
Total events: 387 (Eplerenone), 152 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=2(P=0.77); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					



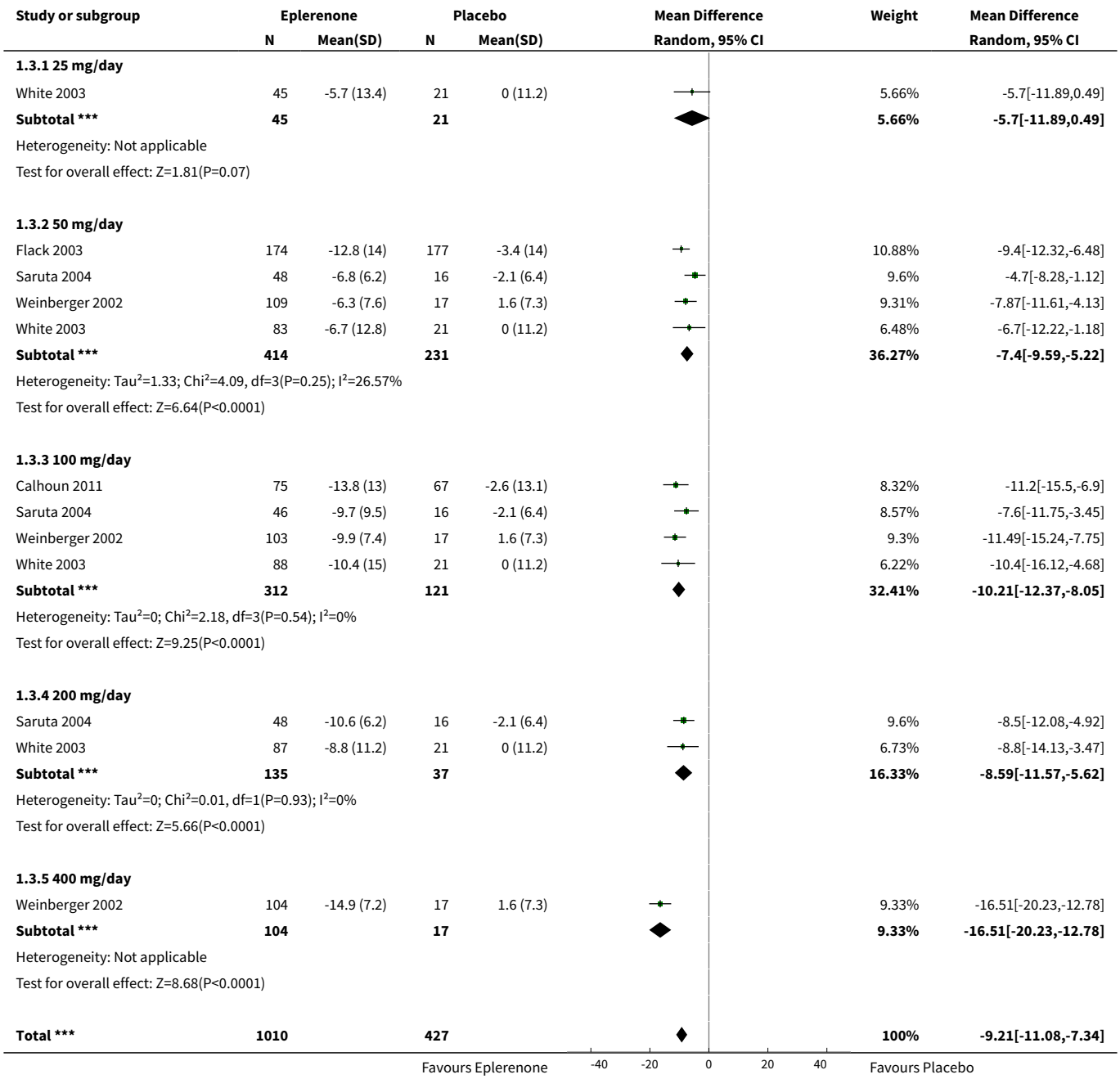
Analysis 1.2. Comparison 1 Eplerenone monotherapy vs placebo, Outcome 2 Adverse event leading to withdrawal.

Study or subgroup	Eplerenone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Flack 2003	6/182	6/181		55.37%	0.99[0.31,3.14]
Weinberger 2002	8/316	1/53		15.89%	1.35[0.17,11.02]
White 2003	8/310	2/90		28.74%	1.17[0.24,5.59]





Analysis 1.3. Comparison 1 Eplerenone monotherapy vs placebo, Outcome 3 Systolic blood pressure.



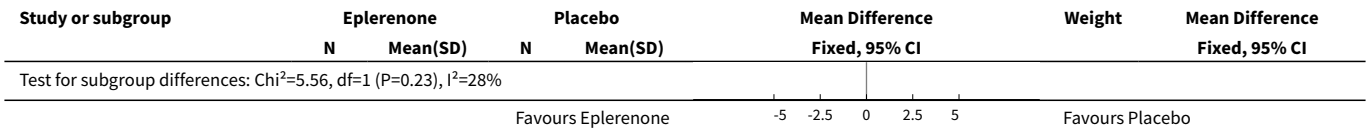
Study or subgroup	Eplerenone N	Eplerenone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=6.18; Chi²=26.5, df=11(P=0.01); I²=58.49%							
Test for overall effect: Z=9.63(P<0.0001)							
Test for subgroup differences: Chi²=19.33, df=1 (P=0), I²=79.31%							

Favours Eplerenone Favours Placebo

Analysis 1.4. Comparison 1 Eplerenone monotherapy vs placebo, Outcome 4 Diastolic blood pressure.

Study or subgroup	Eplerenone N	Eplerenone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 25 mg/day							
White 2003	45	-3.7 (6.7)	21	-1.7 (7.5)		5.13%	-2[-5.75,1.75]
Subtotal ***	**45**		**21**			**5.13%**	**-2[-5.75,1.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.05(P=0.3)							
1.4.2 50 mg/day							
Flack 2003	174	-10.3 (8.7)	177	-5.3 (8.6)		21.82%	-5[-6.82,-3.18]
Saruta 2004	48	-5.1 (4.2)	16	-3 (4.2)		12.61%	-2.1[-4.49,0.29]
Weinberger 2002	109	-4.4 (7.3)	17	-1.1 (7.3)		5.18%	-3.35[-7.08,0.38]
White 2003	83	-4.6 (5.5)	21	-1.7 (7.5)		6.22%	-2.9[-6.3,0.5]
Subtotal ***	**414**		**231**			**45.83%**	**-3.73[-4.98,-2.48]**
Heterogeneity: Tau²=0; Chi²=3.94, df=3(P=0.27); I²=23.81%							
Test for overall effect: Z=5.84(P<0.0001)							
1.4.3 100 mg/day							
Calhoun 2011	75	-7.9 (8.7)	67	-2.6 (8.6)		8.91%	-5.3[-8.14,-2.46]
Saruta 2004	46	-6.9 (5.4)	16	-3 (4.2)		10.61%	-3.9[-6.5,-1.3]
Weinberger 2002	103	-6.2 (7.4)	17	-1.1 (7.3)		5.14%	-5.08[-8.82,-1.34]
White 2003	88	-6.3 (7.5)	21	-1.7 (7.5)		5.69%	-4.6[-8.16,-1.04]
Subtotal ***	**312**		**121**			**30.34%**	**-4.64[-6.18,-3.1]**
Heterogeneity: Tau²=0; Chi²=0.57, df=3(P=0.9); I²=0%							
Test for overall effect: Z=5.91(P<0.0001)							
1.4.4 200 mg/day							
Saruta 2004	48	-7.5 (8.3)	16	-3 (4.2)		7.3%	-4.5[-7.64,-1.36]
White 2003	87	-5.4 (5.6)	21	-1.7 (7.5)		6.22%	-3.7[-7.1,-0.3]
Subtotal ***	**135**		**37**			**13.52%**	**-4.13[-6.44,-1.83]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.73); I²=0%							
Test for overall effect: Z=3.51(P=0)							
1.4.5 400 mg/day							
Weinberger 2002	104	-8.8 (7.2)	17	-1.1 (7.3)		5.18%	-7.69[-11.42,-3.97]
Subtotal ***	**104**		**17**			**5.18%**	**-7.69[-11.42,-3.97]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=4.05(P<0.0001)							
Total ***	**1010**		**427**			**100%**	**-4.18[-5.03,-3.33]**
Heterogeneity: Tau²=0; Chi²=10.18, df=11(P=0.51); I²=0%							
Test for overall effect: Z=9.66(P<0.0001)							

Favours Eplerenone Favours Placebo



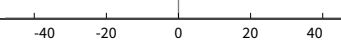
Comparison 2. Eplerenone direct dose comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic dose response	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 50 mg/day vs 25 mg/day	1	128	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.78, 3.78]
1.2 100 mg/day vs 25 mg/day	1	133	Mean Difference (IV, Fixed, 95% CI)	-4.7 [-9.72, 0.32]
1.3 200 mg/day vs 25 mg/day	1	132	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-7.67, 1.47]
1.4 100 mg/day vs 50 mg/day	3	445	Mean Difference (IV, Fixed, 95% CI)	-4.27 [-5.94, -2.61]
1.5 200 mg/day vs 50 mg/day	2	234	Mean Difference (IV, Fixed, 95% CI)	-5.33 [-7.87, -2.78]
1.6 400 mg/day vs 50 mg/day	1	213	Mean Difference (IV, Fixed, 95% CI)	-8.64 [-10.63, -6.66]
1.7 200 mg/day vs 100 mg/day	2	269	Mean Difference (IV, Fixed, 95% CI)	0.12 [-2.38, 2.63]
1.8 400 mg/day vs 100 mg/day	1	207	Mean Difference (IV, Fixed, 95% CI)	-5.02 [-7.00, -3.03]
2 Diastolic dose response	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 50 mg/day vs 25 mg/day	1	128	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.19, 1.39]
2.2 100 mg/day vs 25 mg/day	1	133	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-5.11, -0.09]
2.3 200 mg/day vs 25 mg/day	1	132	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.99, 0.59]
2.4 100 mg/day vs 50 mg/day	3	477	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-2.88, -0.61]
2.5 200 mg/day vs 50 mg/day	2	266	Mean Difference (IV, Fixed, 95% CI)	-1.26 [-2.66, 0.15]
2.6 400 mg/day vs 50 mg/day	1	213	Mean Difference (IV, Fixed, 95% CI)	-4.34 [-6.30, -2.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 200 mg/day vs 100 mg/day	2	269	Mean Difference (IV, Fixed, 95% CI)	0.41 [-1.20, 2.02]
2.8 400 mg/day vs 100 mg/day	1	207	Mean Difference (IV, Fixed, 95% CI)	-2.61 [-4.59, -0.63]

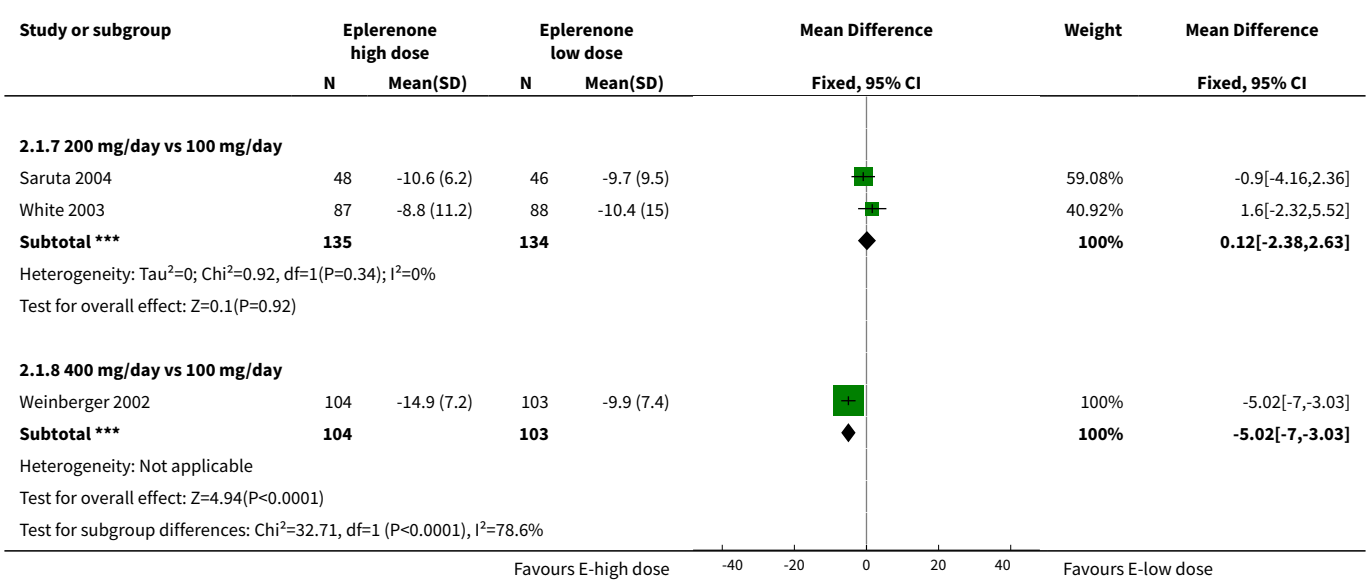
Analysis 2.1. Comparison 2 Eplerenone direct dose comparisons, Outcome 1 Systolic dose response.

Study or subgroup	Eplerenone high dose N	Eplerenone high dose Mean(SD)	Eplerenone low dose N	Eplerenone low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 50 mg/day vs 25 mg/day							
White 2003	83	-6.7 (12.8)	45	-5.7 (13.4)		100%	-1[-5.78,3.78]
Subtotal ***	**83**		**45**			**100%**	**-1[-5.78,3.78]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
2.1.2 100 mg/day vs 25 mg/day							
White 2003	88	-10.4 (15)	45	-5.7 (13.4)		100%	-4.7[-9.72,0.32]
Subtotal ***	**88**		**45**			**100%**	**-4.7[-9.72,0.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.84(P=0.07)							
2.1.3 200 mg/day vs 25 mg/day							
White 2003	87	-8.8 (11.2)	45	-5.7 (13.4)		100%	-3.1[-7.67,1.47]
Subtotal ***	**87**		**45**			**100%**	**-3.1[-7.67,1.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.33(P=0.18)							
2.1.4 100 mg/day vs 50 mg/day							
Saruta 2004	46	-9.7 (9.5)	16	-2.1 (6.4)		16.04%	-7.6[-11.75,-3.45]
Weinberger 2002	103	-9.9 (7.4)	109	-6.3 (7.6)		68.03%	-3.63[-5.64,-1.61]
White 2003	88	-10.4 (15)	83	-6.7 (12.8)		15.93%	-3.7[-7.87,0.47]
Subtotal ***	**237**		**208**			**100%**	**-4.27[-5.94,-2.61]**
Heterogeneity: Tau^2=0; Chi^2=2.93, df=2(P=0.23); I^2=31.82%							
Test for overall effect: Z=5.04(P<0.0001)							
2.1.5 200 mg/day vs 50 mg/day							
Saruta 2004	48	-10.6 (6.2)	16	-2.1 (6.4)		50.44%	-8.5[-12.08,-4.92]
White 2003	87	-8.8 (11.2)	83	-6.7 (12.8)		49.56%	-2.1[-5.71,1.51]
Subtotal ***	**135**		**99**			**100%**	**-5.33[-7.87,-2.78]**
Heterogeneity: Tau^2=0; Chi^2=6.08, df=1(P=0.01); I^2=83.54%							
Test for overall effect: Z=4.1(P<0.0001)							
2.1.6 400 mg/day vs 50 mg/day							
Weinberger 2002	104	-14.9 (7.2)	109	-6.3 (7.6)		100%	-8.64[-10.63,-6.66]
Subtotal ***	**104**		**109**			**100%**	**-8.64[-10.63,-6.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.53(P<0.0001)							

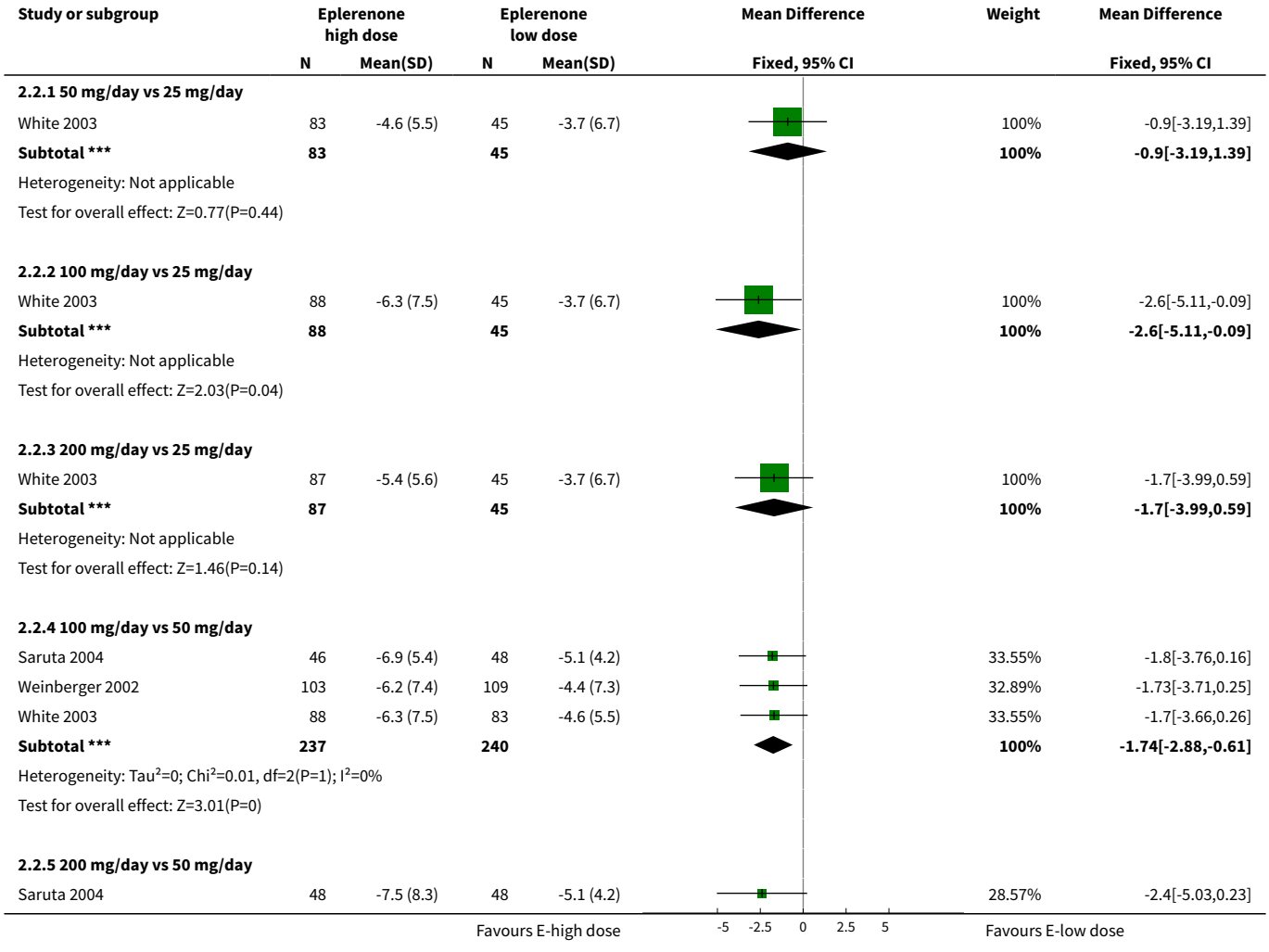


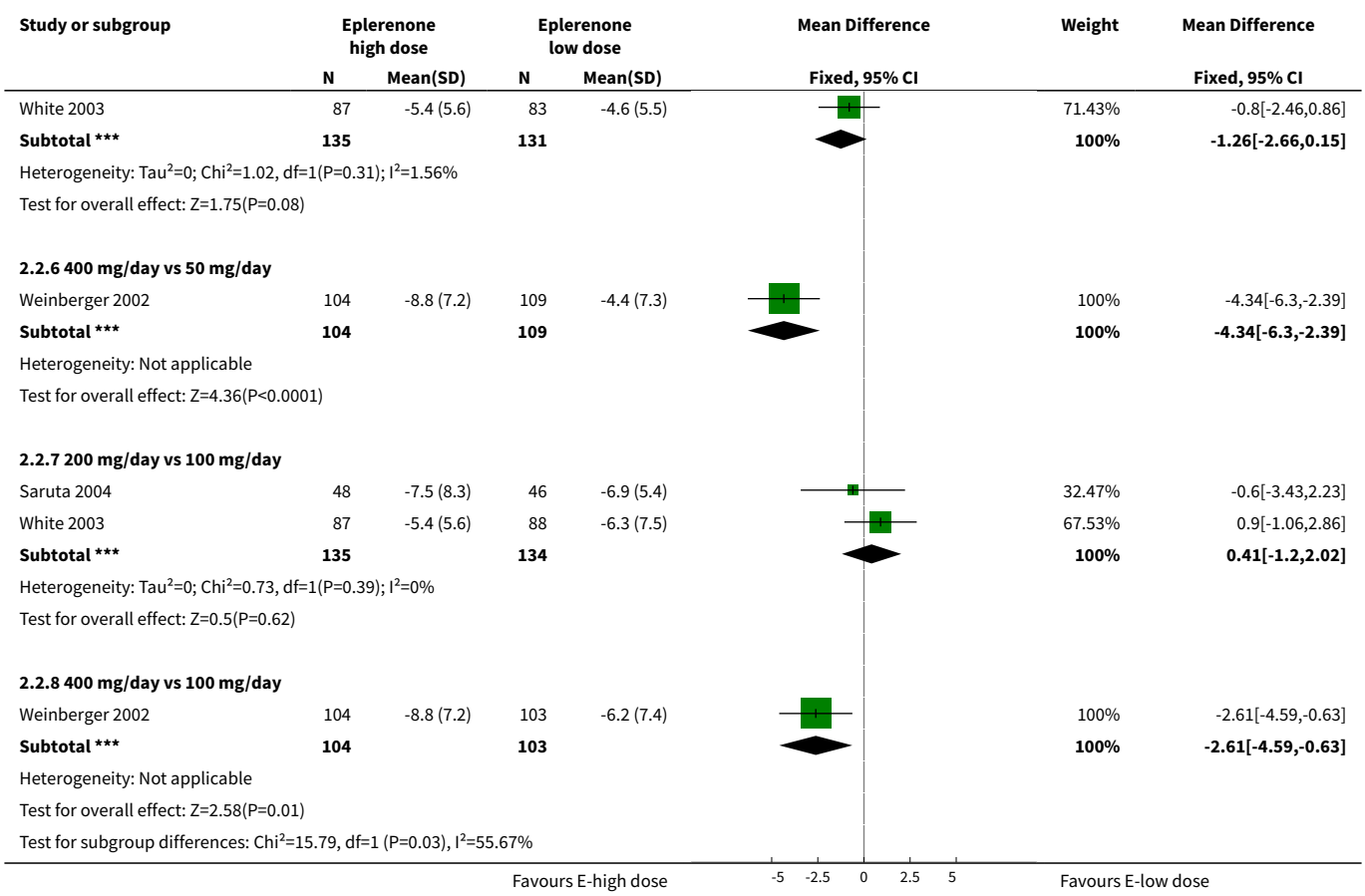
Favours E-high dose

Favours E-low dose



Analysis 2.2. Comparison 2 Eplerenone direct dose comparisons, Outcome 2 Diastolic dose response.





APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Date: 3 March 2016

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1 eplerenon$.mp. (951)

2 (epoxymexrenone or inspra).mp. (32)

3 1 or 2 (955)

4 hypertension/ (206970)

5 hypertens$.tw. (322830)

6 exp blood pressure/ (260668)

7 (blood pressure or bloodpressure).tw. (223000)

8 or/4-7 (616055)

9 randomized controlled trial.pt. (407468)

10 controlled clinical trial.pt. (90116)

11 randomized.tw. (326346)

12 placebo.tw. (159611)

13 drug therapy/ (28738)

14 randomly.tw. (216170)

15 trial.tw. (372508)

16 groups.tw. (1387094)

17 or/9-16 (2077578)

18 animals/ not (humans/ and animals/) (4161070)

19 17 not 18 (1710532)

20 3 and 8 and 19 (92)

21 remove duplicates from 20 (92)

Database: Cochrane Central Register of Controlled Trials <2016, Issue 3> via Cochrane Register of Studies Online

Search Date: 3 March 2016

#1 eplerenon* 152

#2 (epoxymexrenone or inspra) 2

#3 #1 OR #2 152

#4 MESH DESCRIPTOR Hypertension 13753

#5 hypertens*:TI,AB 31403

#6 MESH DESCRIPTOR blood pressure EXPLODE ALL TREES 24184

#7 (blood pressure or bloodpressure or bp) 55509

#8 #4 OR #5 OR #6 OR #7 70392

#9 #3 AND #8 73

Database: Embase <1974 to 2016 March 02>

Search Date: 3 March 2016

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1 eplerenon$.mp. (3697)

2 (epoxymexrenone or inspra).mp. (183)

3 or/1-2 (3699)

4 exp hypertension/ (563188)

5 hypertens$.tw. (495963)

6 exp blood pressure/ (454413)

7 (blood pressure or bloodpressure).mp. (496246)

8 or/4-7 (1067177)

9 randomized controlled trial/ (396252)

10 crossover procedure/ (46218)

11 double-blind procedure/ (128975)

12 random$.tw. (1059968)

13 (crossover$ or cross-over$).tw. (80579)

14 placebo$.tw. (233767)

15 (doubl$ adj blind$).tw. (165925)

16 allocat$.tw. (101519)

17 comparison.ti. (354702)

18 trial.ti. (199337)

19 or/9-18 (1697693)

20 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5789426)

21 19 not 20 (1469922)

22 3 and 8 and 21 (270)

23 remove duplicates from 22 (266)

Database: Cochrane Hypertension Specialised Register

Search Date: 3 March 2016

#1 (eplerenon* or epoxymexrenone or inspra)

#2 RCT:DE

#3 (Review OR Meta-Analysis):MISC2

#4 #2 OR #3 #5 #1 AND #4 (61)

Database: ClinicalTrials.gov

Search Date: 3 March 2016

Study type: Interventional

Studies Conditions: hypertension

Interventions: eplerenone

Search terms: randomized (18)

HISTORY

Protocol first published: Issue 2, 2011
Review first published: Issue 2, 2017

Date	Event	Description
9 February 2016	Amended	Updated protocol with most recent guidelines and references. New authors added.

CONTRIBUTIONS OF AUTHORS

All eight authors were responsible for searching for trials, data extraction, data analyses, interpretation of data, and writing/editing of the final report.

DECLARATIONS OF INTEREST

Sarah C Masson: none known.

Aaron M Tejani: none known.

Sarah N Stabler: none known.

Matthew P Tsang: none known.

Anthony Tung: none known.

Angus TV Kinkade: none known.

Tina SC Tam: none known.

May HY Wu: none known.

SOURCES OF SUPPORT

Internal sources

- Fraser Health Authority, Canada.
- Cochrane Hypertension Group, Canada.

  Assistance in the electronic search

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*administration & dosage] [adverse effects]; Blood Pressure [drug effects]; Eplerenone; Essential Hypertension; Hypertension [complications] [*drug therapy]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Spironolactone [administration & dosage] [adverse effects] [*analogs & derivatives]

MeSH check words

Adult; Female; Humans; Male; Middle Aged