Withdrawal of antihypertensive drugs in older people

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ABSTRACT

Background

Hypertension is an important risk factor for subsequent cardiovascular events, including ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Overall, the use of antihypertensive medications has led to reduction in cardiovascular disease, morbidity rates and mortality rates. However, the use of antihypertensive medications is also associated with harms, especially in older people, including the development of adverse drug reactions, drug-drug interactions and can contribute to increasing medication-related burden. As such, discontinuation of antihypertensives may be considered and appropriate in some older people.

Objectives

To investigate whether withdrawal of antihypertensive medications is feasible, and evaluate the effects of withdrawal of antihypertensive medications on mortality, cardiovascular outcomes, hypertension and quality of life in older people.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials up to April 2019: the Cochrane Hypertension Specialised Register, CENTRAL (2019, Issue 3), Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov. We also conducted reference checking, citation searches and, when appropriate, contacted study authors to identify any additional studies. The searches had no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) of withdrawal versus continuation of antihypertensive medications used for hypertension or primary prevention of cardiovascular disease in older adults (defined as 50 years and over). Participants were eligible if they lived in the community, residential aged care facilities, or were based in hospital settings. We sought to include trials looking at the complete withdrawal of the antihypertensive medication, and those focusing on a dose reduction of the antihypertensive medicine.

Data collection and analysis

We compared the intervention of discontinuing or reducing antihypertensive medication to usual treatment using mean differences (MD) and 95% confidence intervals (95% CIs) for continuous variables and we used Peto odds ratios (ORs) and 95% CI for binary variables. Our primary outcomes included: mortality, myocardial infarction, development of adverse drug reactions or adverse drug withdrawal reactions. Secondary outcomes included: blood pressure, hospitalisation, stroke, success of withdrawing from antihypertensives, quality of life, and falls. Two authors independently, and in duplicate, conducted all stages of study selection, data extraction and quality assessment.

Main results

Six RCTs met the inclusion criteria and were included in the review (1073 participants). Study duration and follow-up ranged from 4 weeks to 56 weeks. Meta-analysis of studies showed that, in the discontinuation group compared to continuation, the odds for all-cause mortality were 2.08 (95% CI 0.79 to 5.46; low certainty of evidence), for myocardial infarction 1.86 (95% CI 0.19 to 17.98; very low certainty of evidence) and for stroke 1.44 (95% CI 0.25 to 8.35; low certainty of evidence). Blood pressure was higher in the discontinuation group than the continuation group (systolic blood pressure: MD = 9.75 mmHg, 95% CI 7.33 to 12.18; and diastolic blood pressure: MD = 3.5 mmHg, 95% CI 1.82 to 5.18; low certainty of evidence). For the development of adverse events, meta-analysis was not possible; antihypertensive discontinuation did not appear to increase the risk of adverse events and may lead to resolution of adverse drug reactions, although eligible studies had limited reporting of adverse effects of drug withdrawal (very low certainty of evidence). One study reported hospitalisation with an odds ratio of 0.83 for discontinuation compared to continuation (95% CI 0.33 to 2.10; low certainty of evidence). No studies were identified which reported falls. Between 10.5% and 33.3% of participants in the discontinuation group compared to 9% to 15% in the continuation group experienced raised blood pressure or other clinical criteria (as pre-defined by the studies) that would require restarting of therapy/removal from the study. The sources of bias included selective reporting (reporting bias), lack of blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and lack of blinding of participants and personnel (performance bias).

Authors' conclusions

There is no evidence of an effect of discontinuing compared with continuing antihypertensives used for hypertension or primary prevention of cardiovascular disease in older adults on all-cause mortality and myocardial infarction. The evidence was low to very low certainty mainly due to small studies and low event rates. These limitations mean that we cannot make any firm conclusions about the effect of deprescribing antihypertensives on these outcomes. Future research should focus on populations with the greatest uncertainty of the benefit:risk ratio for use of antihypertensive medications, such as those with frailty, older age groups and those taking polypharmacy, and measure clinically important outcomes such as falls, quality of life and adverse drug events.

P L A I N   L A N G U A G E   S U M M A R Y

Stopping blood pressure medications in older people

Aim

This review aimed to find out if it is possible to stop blood pressure medications in older people. We also wanted to find out the effects of stopping these medications.

We included adults aged 50 years and over who were taking blood pressure medications for high blood pressure (hypertension) or for prevention of heart diseases (primary prevention). We excluded studies with people who had previously had a heart attack, stroke or other heart disease (secondary prevention).

We compared stopping or reducing the dose of blood pressure medications with continuing blood pressure medications.

Background

High blood pressure, also known as hypertension, is a risk factor for many diseases, such as heart attack, kidney failure and stroke. While hypertension usually produces no symptoms, keeping blood pressure under control is vital for preserving health and reducing the risk of serious conditions.

Hypertension is often managed with lifestyle and blood pressure (antihypertensive) medications. There are many different types of blood pressure medications available.

Antihypertensives can cause dangerous side effects, such as dizziness and fatigue which might lead to falls. Older people are at greater risk of medication side effects compared to younger people. It is unclear whether the benefits of antihypertensive medications outweigh the harms in older people.

Study characteristics

Our search to April 2019 found six studies, including 1,073 older adults in total. People in the studies had an average age of 58 to 82 years. In three of the studies, the dose of the antihypertensive was slowly lowered before stopping.

Key results

We found that stopping antihypertensive medications is possible in older adults. Most of the older people in the discontinuation groups did not need to restart their medication.

We found low certainty of evidence that stopping antihypertensive medication increased blood pressure by a small amount.

We found low or very low certainty of evidence that stopping blood pressure medications did not increase the risk of having a heart attack, stroke, hospitalisation or death.

We found very low certainty of evidence that stopping blood pressure medications did not increase the risk of adverse events and may resolve side effects, but this was not reported well, and so we were unable to draw conclusions.

None of the studies reported whether stopping blood pressure medications affected falls.

Certa inty of the evidence

We rated the certainty of the evidence using four levels: very low, low, moderate, or high. High certainty evidence means that we are very confident in the results. Very low certainty evidence means that we are very uncertain about the results. We judged the certainty of evidence as very low and low.

Conclusion

It may be safe to stop antihypertensive medications in older people who are taking the medication for high blood pressure or primary prevention of heart disease.

Older adults should not stop any of their medications without talking to a healthcare professional.

Future studies should include older adults who are taking multiple other medications and/or living with frailty.

SUMMARY OF FINDINGS

Summary of findings 1.   Discontinuation by no treatment/placebo of antihypertensives compared to continuation in older people

Discontinuation by no treatment/placebo of antihypertensives compared to continuation in older people

Patient or population: Older adults, 50 years and older
Setting: All settings
Intervention: Discontinuation by no treatment/placebo of antihypertensives
Comparison: Continuation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Continuation	**Risk with Discontinuation by no treatment/placebo of antihypertensives**				
All-cause mortality follow-up: range 12 weeks to 12 months	Study population		OR 2.08 (0.79 to 5.46)	630 (4 RCTs)	⊕⊕⊝⊝ LOW [1][2][3][4]	
	19 per 1,000	40 per 1,000 (15 to 98)				
	Moderate					
	26 per 1,000	52 per 1,000 (20 to 126)				
Myocardial infarction (fatal and nonfatal) follow-up: range 16 weeks to 12 months	Study population		OR 1.86 (0.19 to 17.98)	447 (2 RCTs)	⊕⊝⊝⊝ VERY LOW [5][6]	
	5 per 1,000	9 per 1,000 (1 to 77)				
	Moderate					
	3 per 1,000	5 per 1,000 (1 to 46)				
Hospitalisation follow-up: 16 weeks	Study population		OR 0.83 (0.33 to 2.10)	385 (1 RCT)	⊕⊕⊝⊝ LOW [7]	
	54 per 1,000	45 per 1,000 (18 to 107)				
Stroke (fatal + nonfatal + TIA)	Study population		OR 1.44	524 (3 RCTs)	⊕⊕⊝⊝ LOW [3][8]	

follow-up: range 16 weeks to 12 months	8 per 1,000	11 per 1,000 (2 to 62)	(0.25 to 8.35)		
	Moderate				
	5 per 1,000	8 per 1,000 (1 to 43)			
Systolic blood pressure follow-up: range 12 weeks to 12 months	The mean systolic blood pressure ranged from 123 to 145 mmHg [9]	MD 9.75 mmHg higher (7.33 higher to 12.18 higher)	-	767 (5 RCTs)	⊕⊕⊖⊖ LOW [10] [11] [12]
Diastolic blood pressure: range 12 weeks to 12 months	The mean diastolic blood pressure ranged from 70-95 mmHg [9]	MD 3.5 mmHg higher (1.82 higher to 5.18 higher)	-	768 (5 RCTs)	⊕⊕⊖⊖ LOW [10] [12] [13]
Adverse drug reactions and adverse drug withdrawal reactions (adverse reactions) follow-up: range 12 weeks to 12 months	Overall there was some reversal of adverse drug reactions in the discontinuation group, otherwise no change reported. One study reported no difference in frequency of side effects although data were not shown. One study reported reversal of slight postural drop and improvement in renal function and serum cholesterol in the discontinuation but not the continuation group. One study reported that more participants experienced ankle oedema in the discontinuation than the continuation group, however, statistical significance was not reported. All three studies reported changes in potassium in the discontinuation group.		-	245 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [14] [15]
Falls - not reported	None of the included studies reported on falls or falls risk.		-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

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

[1] Not downgraded for risk of bias: some concern about attrition bias in 2 of the studies (high and uneven drop out rates), not enough to assess as serious but considered when downgrading in other areas.

[2] Not downgraded for inconsistency but considered when downgrading other areas: some concern about heterogeneity due to the difference in mortality rates between Myers 1982 and Maland 1983 but likely explained by differences in populations (Maland's participants were older and recruited from geriatric institutions).

[3] Downgraded one level for imprecision, the total number of events was very low ; additionally, the CI included the null effect and appreciable benefit favouring continuation.

[4] Downgraded one level for indirectness due to concern about the age of the majority of studies relevant for this outcome - standards of care and recommendations for treatment have significantly changed over the past 35 years. Downgrading in this category also took into account the large concern about imprecision (which was downgraded 1, but had considered downgrading 2 steps) as well as potential risk of bias and inconsistency.

[5] Downgraded one level for risk of bias as neither study had blinding of participants or physicians; possible that diagnosis of MI could have been influenced by knowledge of intervention.

[6] Downgraded two levels for imprecision as the total number of events was very low; additionally, the CI included the null effect and appreciable benefit favouring continuation.

[7] Downgraded two levels for imprecision as the total number of events was very low; additionally, the CI included the null effect and appreciable benefit favouring discontinuation.

[8] Downgraded one level for indrectness due to concern about the age of the majority of studies relevant for this outcome - standards of care and recommendations for treatment have significantly changed over the past 35 years. Downgrading in this category also took into account the large concern about imprecision (which was downgraded 1, but had considered downgrading 2 steps)..

[9] Range of BP at end of follow-up period in continuation group of included studies.

[10] Downgraded one level for risk of bias due to concern about lack of blinding of participants and physicians in two of the studies, uneven dropouts in two of the studies and reporting bias in one of the studies.

[11] Downgraded one level for inconsistency due to substantial heterogeneity, subgroup analyses based on duration of follow-up and class of medication was not able to explain heterogeneity, and no other cause identified.

[12] Some concern about indirectness as BP is a surrogate marker, also the majority of studies are more than 35 years old. Did not downgrade in this category, however contributed to the decision to downgrade in the 'Risk of bias' category.

[13] Downgraded one level for inconsistency; duration of follow-up was able to explain some of the inconsistency, however, heterogeneity remained in the subgroup with a duration of follow-up 12 months or greater.

[14] Downgraded two levels for risk of bias due to very serious concern about lack of blinding, attrition bias and poor detection and reporting of outcome.

[15] Downgraded one level for imprecision due to small sample size and number of events.

TIA: Transient ischaemic attack

BACKGROUND

Description of the condition

Hypertension or high blood pressure (BP) increases with age, and is prevalent in over two-thirds of people aged over 60 (Fryar 2017). Hypertension is a major risk factor for subsequent cardiovascular events including ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death (NICE 2019). In older adults, the use of antihypertensive medications has led to reductions in overall cardiovascular disease (CVD), morbidity rates and mortality rates in people with high BP (Ikeda 2014; Musini 2019).

Ensuring appropriate use of antihypertensive drugs can be challenging, especially in an older population with increasing age-associated pathologies, including polypharmacy, multi-morbidity, frailty, orthostatic hypotension (a significant decrease in blood pressure when changing from a sitting or lying position to standing), falls and cognitive impairment (Parekh 2017). Antihypertensive medications can increase the risk of adverse drug reactions (ADRs), and cause undesired metabolic effects such as hypokalaemia (low potassium in the blood), hyperkalaemia (high potassium in the blood), hyperglycaemia (high blood sugar level) or hyperuricaemia (excess of uric acid in the blood). Blood pressure lowering in older people may decrease cerebral autoregulation resulting in worsening of cognition, and a higher BP may be preferred to ensure adequate cerebral blood flow (Goshgarian 2019). Antihypertensives may contribute to polypharmacy, which is the use of multiple medicines simultaneously in an individual patient, and has been widely documented as a risk factor for ADRs, drug-disease and drug-drug interactions as well as increased morbidity and mortality, and costs (Reeve 2014; Steinman 2006; Wastesson 2018). Reducing the number of medications taken including antihypertensive medications by deprescribing (i.e. planned and supervised withdrawal of medications that are inappropriate), may therefore lead to reduced adverse effects and improved quality of life (QoL) in older people (Gnjidic 2014; Reeve 2014; Scott 2015).

Description of the intervention

Hypertension is treated with lifestyle and medications. Healthy lifestyle measures include a diet low in salt, regular exercise, weight loss, safe alcohol consumption, avoidance of excessive caffeine consumption, and smoking cessation. Several antihypertensive classes can be used either alone or in combination, including angiotensin receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics, most commonly thiazide diuretics. Other medication classes can be added if hypertension is resistant (National Heart Foundation of Australia 2016; NICE 2019; Whelton 2018; Williams 2018). However, over time, the benefits and harms of a medication in an individual can change, making medications that were once appropriate, now inappropriate (that is, the likely harms outweigh the likely benefits in the individual, including where the benefits no longer align with the person's goals of care) (Reeve 2015; Reeve 2017; Scott 2015).

Withdrawal of antihypertensive medications can either be complete (immediate) discontinuation of medications or dose reduction with or without intermittent therapy reduction strategies, also known as tapered withdrawal (gradual withdrawal according to a predefined dosing schedule or following clinical response) (Ekbom 1994; Reeve 2014). In the context of this review, we included and evaluated randomised controlled trials (RCTs) that withdrew antihypertensive medications in older adults, either by immediate discontinuation or by tapering interventions.

How the intervention might work

Withdrawal of antihypertensive drugs in older people, prescribed one or more antihypertensive medications for hypertension or primary prevention of cardiovascular disease, may theoretically cause a reduction in undesired metabolic effects and reduce medication errors, drug-drug and drug-disease interactions, and ADRs (that may occur as a result of continued use of antihypertensive medications). Additional possible positive effects of antihypertensive drug withdrawal may include a reduction in the risk of falls, reduction in compromised cerebral blood flow and hypoperfusion (reduced blood flow) (Froom 1997; Goshgarian 2019; Scott 2019). However, withdrawal of antihypertensive medications may also cause an increase in BP and may increase the risk of cardiovascular outcomes or mortality (Ekbom 1994; Ikeda 2014; NICE 2019).

Why it is important to do this review

There is substantial evidence that the use of antihypertensive medications within the context of polypharmacy and multi-morbidity can lead to increased risk of harm in older people (Scott 2019; Woolcott 2009). To inform the appropriateness of withdrawing antihypertensive medications in older people, we thus proposed to critically evaluate the evidence in relation to the safety and efficacy of withdrawal of antihypertensive medications to inform clinical decisions and future research. Previous systematic reviews and meta-analyses included multiple medication classes without a primary focus on antihypertensive withdrawal interventions (Iyer 2008), were conducted in the 1990s (Froom 1997), focused on all ages, not specifically on older people (Nelson 2001; Van der Wardt 2017), or primarily focused on the effect of medication withdrawal interventions on cognition in older people (Jongstra 2016). Thus, this review provides up-to-date evidence and investigates a number of clinically relevant outcomes of antihypertensive withdrawal in older people.

OBJECTIVES

To investigate whether withdrawal of antihypertensive medications is feasible, and evaluate the effects of withdrawal of antihypertensive medications on mortality, cardiovascular outcomes, hypertension and quality of life in older people.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. All other study types were excluded e.g. observational studies, case series.

Types of participants

Participants were adults aged 50 years and over prescribed one or more antihypertensive medication(s) for hypertension or primary prevention of cardiovascular disease living in the community, residential aged care facilities or in hospital settings. The cut-off of 50 years to define 'older adults' was chosen to maximise inclusion

of relevant older studies and studies from developing countries (Shenkin 2017).

To be eligible, either all participants had to be aged 50 years or older, or results for participants aged 50 years and older had to be presented in a separate subgroup analysis, or the majority of participants had to be 50 years or older (as determined by looking at mean/median age and standard deviation (SD)/interquartile range (IQR) (to be included, the mean age minus the SD must be ≥ 50 years, or if IQR, three-quarters of participants must be ≥ 50 years old, or the article reported the number of people ≥ 50 years old).

Studies were included if the reported indication in the study was hypertension or primary prevention of cardiovascular disease and less than 20% of the population had cardiovascular disease at baseline.

Types of interventions

Included studies assessed withdrawal of antihypertensive medications in older adults prescribed for hypertension or primary prevention of cardiovascular disease. Withdrawal of medications may be through abrupt withdrawal, tapering to complete withdrawal or dose reduction. The control intervention included no withdrawal of antihypertensive medications (i.e. continuation).

The following antihypertensive medications were included:

- diuretics which act primarily by blocking reabsorption of sodium at four major sites in the nephron. Different classes of diuretics act at different sites. Loop diuretics (e.g. furosemide, torsemide) act in the thick ascending limb of the loop of Henle. Thiazide-type diuretics (e.g. hydrochlorothiazide, chlorthalidone, indapamide) act in the distal tubule and connecting segment. Potassium-sparing diuretics (e.g. amiloride, triamterene) increase diuresis, but without causing potassium to be lost from the body. Aldosterone receptor antagonists (e.g. spironolactone, eplerenone) stop the entry of aldosterone into the principal cells of the collecting duct and late distal tubule of the nephron, which prevents sodium and water retention;
- beta-blockers (e.g. atenolol, carvedilol) block the effects of catecholamines at receptor sites in the heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Beta-blockers reduce BP by blocking the effects of catecholamine on the heart and blood vessels;
- ACE inhibitors (e.g. captopril, enalapril) act by blocking the renin-angiotensin system; specifically, they block conversion of angiotensin I to angiotensin II and bradykinin. ACE inhibitors reduce the effects of angiotensin II-induced vasoconstriction, sodium retention and aldosterone release;
- calcium channel blockers (e.g. amlodipine, felodipine) act by blocking inward current of calcium via L-type calcium channels. Calcium channel blockers lower BP by blocking the effects of calcium on blood vessels;
- angiotensin II receptor antagonists (e.g. candesartan, irbesartan) act by blocking binding of angiotensin II to type 1 angiotensin (AT_1) receptors. This leads to reduction in angiotensin II-induced vasoconstriction, sodium reabsorption and aldosterone release; blood vessels dilate leading to reduction in BP;

- renin inhibitors (e.g. aliskiren) prevent the conversion of angiotensinogen to angiotensin I by binding to the S3^{bp} binding site of renin.

Types of outcome measures

Primary outcomes

- Mortality (all-cause mortality, cardiovascular mortality).
- Myocardial infarction (fatal and non-fatal).
- Adverse drug reactions and adverse drug withdrawal reactions.

Secondary outcomes

- Blood pressure (BP), including systolic and diastolic BP, before and after withdrawal of antihypertensive drugs and mean arterial pressure.
- Hospitalisation (all-cause, cardiovascular hospitalisation, heart failure hospitalisation).
- Stroke (fatal and non-fatal, ischaemic and haemorrhagic, transient ischaemic attack).
- Success (rate) of withdrawal from antihypertensive drugs over the short term (12 months or less) and long term (greater than 12 months). Success (rate) will be defined as the ability of the participant to complete the study having experienced withdrawal from antihypertensive medications and resisted restarting existing treatment given before withdrawal.
- Quality of life (QoL) of participants, carers, families or a combination, measured with validated QoL instruments (e.g. EuroQol - five dimensions questionnaire (EQ-5D), Short Form - six dimensions (SF-6D)).
- Falls

There was no restriction on duration of follow-up for any of the outcomes.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist searched the following databases without language, publication year or publication status restrictions:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 22 May 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL, 2019, Issue 3) via the Cochrane Register of Studies (CRS-Web) (searched 22 April 2019);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 22 April 2019);
- Embase Ovid (from 1974 onwards) (searched 22 April 2019);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 22 April 2019);
- World Health Organisation International Clinical Trials Registry Platform (http:// https://apps.who.int/trialsearch) (searched 22 April 2019).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the highly sensitivity and precision-maximising search strategy

designed by Cochrane for identifying randomised controlled trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.d. (Higgins 2011)). We present search strategies for major databases in Appendix 1.

Searching other resources

The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE and Embase) for systematic reviews and Epistemonikos to retrieve published systematic reviews related to this review title to identify additional relevant trials. The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment for information of adverse effects relevant to this review.

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

We contacted experts/organisations in the field to obtain additional information on relevant trials.

We contacted trial authors for clarification and further data if trial reports were unclear.

Data collection and analysis

Selection of studies

Two review authors (out of ER, WT, MS, AT, TM, IH, VJ, and DG) independently conducted article screening for relevance and adherence to inclusion criteria. If studies did not meet the inclusion criteria, we excluded them and recorded reasons for exclusion. Disagreements were resolved through consultation with a third review author.

Data extraction and management

Two review authors (out of ER, WT, MS, AT, and DG) independently performed data extraction. Disagreements were resolved by consultation with a third review author.

The summary statistics required for each trial and outcome for continuous data included the values at different time points, mean change from baseline or difference between intervention and control group, the standard deviation and the number of participants in each group (discontinuation and continuation). The baseline assessments were defined as the latest available assessment between the discontinuation and continuation group, or from baseline. For binary outcomes (e.g. success rate), the number and percentage in (each) group were sought.

We extracted the following data from the studies and presented them in a summary table:

- author, year of publication, country;
- type of intervention;
- antihypertensive medication withdrawn;
- withdrawal method (immediate or tapered);

For each outcome measure, we extracted data as per the primary analysis presented in each of the studies.

Assessment of risk of bias in included studies

Two review authors (out of ER, WT, MS, AD, and DG) independently assessed the risk of bias in the included studies using the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Sterne 2014). We assessed the risk of bias in terms of internal validity criteria for RCTs including random sequence generation (randomisation), allocation concealment, participant and study personnel blinding, blinding of outcome assessors, level of incomplete outcome data, selective reporting and other risks of bias that may be relevant (Higgins 2011; Sterne 2014). Disagreements were resolved through consultation with a third review author, when necessary.

Measures of treatment effect

Studies may or may not utilise similar rating scales in outcome assessment. For this reason, for continuous outcomes, we used the mean difference (MD) when the collective studies utilised identical scales of rating or tests. We planned to use the standardised mean difference (SMD) if dissimilar scales of rates or tests were used. In the case of binary outcomes such as mortality, we used a Peto odds ratios (ORs) to measure the treatment effect. We also calculated 95% confidence intervals (CIs).

Unit of analysis issues

If there were any cluster RCTs, we planned to determine if the risk of unit of analysis error was dealt with appropriately. Where the analysis was carried out correctly taking into account the clustering design, we planned to consider the studies for meta-analysis and use the reported effect sizes and standard errors. Where the analysis was incorrect (i.e. not taking the clustering design into account), we planned to apply an interclass correlation (Higgins 2011). However, no cluster RCTs were found.

Dealing with missing data

We contacted the corresponding author of included studies in the event of missing data that would compromise the ability of the review authors to examine the data and eligibility for study exclusion/inclusion in the final analysis.

Assessment of heterogeneity

We performed meta-analysis where studies were satisfactorily homogenous in terms of interventions, outcomes and participants. In the evaluation of heterogeneity, we determined clinical heterogeneity by review author opinion and used an I^2 test to determine statistical heterogeneity. An I^2 value higher than 50% was considered as evidence for the presence of substantial heterogeneity of the studies. If substantial heterogeneity was present, we aimed to investigate the reasons for the presence of heterogeneity through subgroup analysis.

Assessment of reporting biases

Two review authors (out of ER, DG, MS, AT, and WT) independently assessed the risk of reporting bias in the included studies following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements through consultation with a third review author.

Data synthesis

We synthesised data for each study outcome separately using Review Manager 5 (RevMan 2014), and we undertook meta-analyses for outcomes reported in multiple studies.

We compared outcome measures for binary data utilising Peto odds ratios, due to the rare nature of the primary outcomes, and 95% CI. This necessitated the use of the fixed effect model. For continuous variables or data, we utilised mean differences and 95% CI.

Subgroup analysis and investigation of heterogeneity

Where there were two or more studies, we performed subgroup analysis of medications within antihypertensive medication classes (e.g. ACE inhibitors and diuretics) and based on duration of follow-up (less than 12 months versus 12 months or longer) if sufficient and meaningful data were available. We used class of medication and duration of follow-up subgroups when investigating heterogeneity. Additionally, we intended to conduct subgroups analyses for age group (50 to 65 years, over 65 to 80 years, over 80 years) and gender (men and women). However, this was not possible as data were not reported separately for these groups.

Sensitivity analysis

We intended to perform sensitivity analysis to consider how the results of any meta-analyses undertaken changed under different assumptions, related to the reasons for these effects. More specifically, we intended to conduct a sensitivity analysis on the choice of utilising a random-effects model (Higgins 2011). However, we were unable to perform any sensitivity analyses due to the limited data and small number of studies identified.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for each outcome (Schünemann 2011a; Schünemann 2011b). We present key findings of the review, including a summary of the data, the magnitude of the effect size and the overall certainty of the evidence, in Summary of findings 1. We preselected the following outcomes for inclusion in the Summary of findings 1: mortality, myocardial infarction, adverse drug reactions, blood pressure (systolic and diastolic), hospitalisation, stroke and incidence of falls.

R E S U L T S

Description of studies

Studies are described in detail in Characteristics of included studies; Characteristics of excluded studies and summarised in Table 1.

Results of the search

A total of 3677 articles were identified. After de-duplication, title and abstract screening, a total of 39 studies were obtained in full text (Figure 1). We excluded 33 articles (Characteristics of excluded studies). No additional eligible studies were found through hand searching of reference lists.

Figure 1.   Study flow diagram.


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┌─────────────────────┐   ┌─────────────────────┐
│ 3698 references     │   │ 0 additional records│
│ imported from       │   │ identified through  │
│ database searches   │   │ other sources       │
│ for screening as    │   │                     │
│ 3689 studies        │   │                     │
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        │ 3677 records after duplicates│
        │ removed                      │
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        │ 3677 studies │ ─────► │ 3637 studies │
        │ screened     │        │ excluded     │
        │ against title│        │              │
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                          ┌─────────────────────┐
                          │ 33 studies excluded  │
                          │ 12 wrong             │
                          │ intervention         │
                          │ 9 wrong patient      │
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                          │ design               │
                          │ 6 one or both        │
                          │ groups had           │
                          │ confounding          │
                          │ treatment (diet,     │
                          │ exercise or other    │
                          │ antihypertensives)   │
        ┌──────────────┐  │ 1 clinical trial     │
        │ 39 studies   │──► registry citation    │
        │ assessed     │  │ 1 protocol paper     │
        │ for full-text│  └─────────────────────┘
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        │ 6 studies    │
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        │ qualitative  │
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        │ 6 studies    │
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        │ (meta-analysis)│
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Included studies

Six studies fulfilled the inclusion criteria, comprising 1073 participants (Characteristics of included studies). Two studies were conducted in the USA (Langford 1984; Maland 1983), two in the Netherlands (Moonen 2015; Walma 1997), one in Canada (Myers 1982) and one in Wales (Burr 1977).

Design

The six studies were parallel-group RCTs. There was a wide range of study duration and follow-up, ranging from four weeks to 56 weeks.

Sample Size

All studies included a relatively small number of participants. Two studies included fewer than 100 participants, and four studies included between 100 and 400 participants.

Study setting and participants

Four studies included participants in general practice or primary care (Langford 1984; Maland 1983; Moonen 2015; Walma 1997), one study included participants in long-stay geriatric wards (Burr 1977), and one study included participants living in a geriatric institution (Myers 1982). Mean age ranged from 57.5 years (Langford 1984) to 82.0 years (Burr 1977). Two studies (Moonen 2015; Walma 1997) did not report overall mean age. With respect to inclusion criteria, overall, trials included different study populations. The study by Burr 1977 included participants using diuretics for over one month with no history of significant cardiovascular events (e.g. congestive cardiac failure). Maland 1983 included participants with an average DBP of 90 mmHg using any antihypertensive medication for 12 months, and no history of major cardiovascular events. Moonen 2015 included participants using any antihypertensive medication with a Mini-Mental State Examination (MMSE) score of 21-27. Walma 1997 included participants using diuretics for six months with no history of acute heart failure.

Interventions

Of six studies included, four included participants taking diuretics (Burr 1977; Maland 1983; Myers 1982; Walma 1997), and two studies included participants taking any antihypertensive medication (Langford 1984; Moonen 2015). The study by Langford 1984 included an additional intervention (diet) with participants stratified by obesity status, however, for this systematic review, we only included the groups which did not have the dietary intervention. The discontinuation plan was specified in three studies (Langford 1984; Moonen 2015; Walma 1997), as outlined in Table 1.

Outcomes

All studies reported at least one of the primary outcomes. All-cause mortality was reported in Burr 1977; Maland 1983; Moonen 2015;

and Myers 1982, with Myers 1982 also reporting cardiovascular mortality. Two studies reported myocardial infarction outcomes (Maland 1983; Moonen 2015), and three studies reported on adverse drug reactions or adverse drug withdrawal reactions (Burr 1977; Maland 1983; Myers 1982). The following secondary outcomes were reported: systolic blood pressure (SBP), five studies (Burr 1977; Maland 1983; Moonen 2015; Myers 1982; Walma 1997); stroke, three studies, (Maland 1983; Moonen 2015; Myers 1982) and success of withdrawal as measured by the ability to remain off the medication, four studies (Langford 1984; Maland 1983; Myers 1982; Walma 1997). Moonen 2015 was the only study to report on the hospitalisation and quality of life (QoL) secondary outcomes. No study reported on falls.

Funding

The trials by Burr 1977, Langford 1984 and Maland 1983 all reported pharmaceutical company support through supply of medications and identical placebos to be used in the study. It was not stated, however, what, if any, other involvement the companies had in the study concept, execution, analysis or reporting. Three studies reported nonpharmaceutical company funding (Moonen 2015; Myers 1982; Walma 1997).

Excluded studies

We excluded 33 publications (reasons for exclusion are shown in Characteristics of excluded studies). Reasons for exclusion were wrong intervention (participants were not randomised to withdraw or continue antihypertensives or withdrawal was temporary); wrong patient population (not older adults or wrong indication); wrong study design (not an RCT); one or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives); clinical trial registry citation of an ineligible study due to wrong patient population; and a protocol paper of an ineligible study due to wrong intervention.

Risk of bias in included studies

See Characteristics of included studies for details of the risk of bias in the included studies; there was variable risk of bias across the studies. Figure 2 and Figure 3 show the percentages of low, unclear and high risk of bias across the different domains and the risk of bias in the different domains of the individual studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
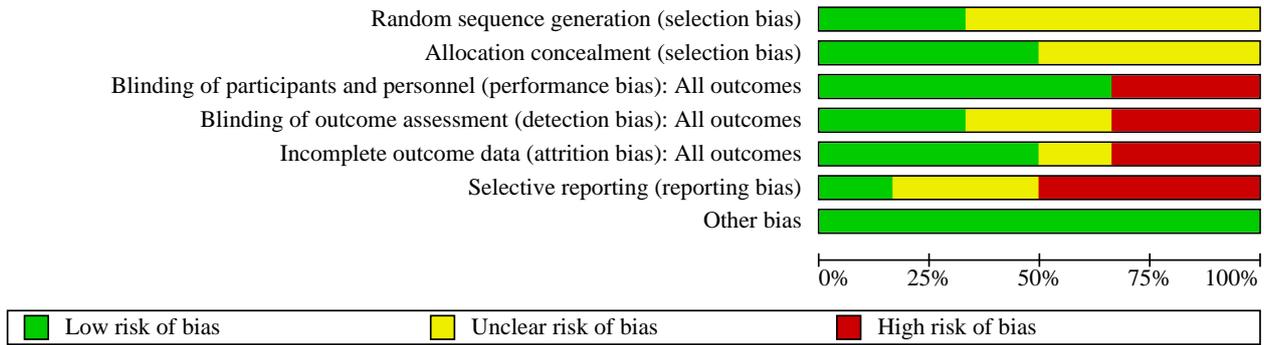
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

All studies were assessed as having low or unclear risk of selection bias. Two studies reported appropriate methods of random sequence generation and were assessed as low risk in this domain (Moonen 2015; Walma 1997). Three studies had a low risk of bias in the allocation concealment domain; Myers 1982 and Walma 1997 used hospital pharmacists to ensure allocation concealment while Moonen 2015 noted a centralised computer randomisation procedure. The majority of studies had an unclear risk of selection bias due to insufficient information.

Blinding

Four of the studies were assessed as having low risk of bias in the blinding of participants and personnel domain as they reported that the study was double-blind and also described some method of blinding, such as using identical placebos for the withdrawal group (Burr 1977; Maland 1983; Myers 1982; Walma 1997). Burr 1977 also noted that the containers were special so as to ensure that personnel were blinded to allocation. Of these four studies, two (Maland 1983; Myers 1982) had insufficient details about blinding of assessors (unclear risk of bias) and one (Walma 1997) was assessed as having low risk of detection bias as it reported that allocation codes were not broken until assessment of the last data had been completed.

The trial by Moonen 2015 did not blind the participants and physicians to treatment group, however, the research personal assessing the outcomes were masked to allocation group. Finally, Langford 1984 didn't specify whether blinding was conducted; external physicians could restart the medication, therefore it is unlikely to have been blinded. As restarting the medication was the primary outcome, this study was assessed as having high risk of performance and detection bias.

Incomplete outcome data

Three studies were assessed as having low risk of attrition bias (Maland 1983; Moonen 2015; Walma 1997), one was unclear (Langford 1984) and the remaining two were high risk (Burr 1977; Myers 1982). Burr 1977 had unclear reporting of dropouts and inconsistent reporting of outcomes particularly for the continuation group, while in the study by Myers 1982, there were uneven dropout rates (with different reasons for dropouts between the groups) and incomplete data reported on their main outcome (BP).

Selective reporting

Only one study was assessed as having low risk of reporting bias (Walma 1997), with the others being unclear (Burr 1977; Myers 1982) or at high risk of bias (Langford 1984; Maland 1983; Moonen 2015). Two studies were assessed as at high risk of bias as outcomes appeared to be reported in unclear and/or select ways with grouping of participants not as per the originally allocated groups (Langford 1984; Maland 1983). For example, Maland 1983 reported BP results for 'reverters' (those whose BP increased to a level requiring restarting of treatment) separately to other participants in the withdrawal group. The third study assessed as being at high risk of reporting bias reported an outcome in their protocol (attached as supplementary data) which was not reported in the main manuscript (Moonen 2015).

Other potential sources of bias

No other potential sources of bias were identified in the studies.

Effects of interventions

See: **Summary of findings 1** Discontinuation by no treatment/placebo of antihypertensives compared to continuation in older people

Primary outcomes

Mortality

Four studies (Burr 1977; Maland 1983; Moonen 2015; Myers 1982) reported all-cause mortality (Analysis 1.1); Maland 1983 and Myers 1982 had up to 12 months follow-up while Burr 1977 had 12 weeks and Moonen 2015 had 16 weeks. All four studies, with a total of 640 participants, were included in a meta-analysis (Figure 4). The odds for all-cause mortality were 2.08 (95% Confidence Interval (CI) = 0.79 to 5.46, I^2 = 0%) of that in the discontinuation group compared to the control group. The certainty of the evidence was low, mostly due to the small number of events in the included studies and also the CI included both the null effect as well as what could be considered an appreciable harm of discontinuation (i.e. favouring continuation).

Figure 4. Forest plot of comparison: 1 Continuation vs discontinuation by no treatment/placebo of antihypertensives, outcome: 1.1 All-cause mortality.

Study or Subgroup	Favours discontinuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Burr 1977 (1)	3	54	1	52	23.6%	2.69 [0.37 , 19.68]	
Maland 1983 (2)	0	31	1	31	6.1%	0.14 [0.00 , 6.82]	
Moonen 2015 (3)	1	199	1	186	12.1%	0.93 [0.06 , 15.02]	
Myers 1982 (4)	8	38	3	39	58.1%	2.94 [0.83 , 10.44]	
Total (95% CI)		**322**		**308**	**100.0%**	**2.08 [0.79 , 5.46]**	
Total events:	12		6				

Heterogeneity: Chi² = 2.53, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable

0.001   0.1   1   10   1000
Favours discontinuation   Favours continuation

Footnotes
(1) 12 weeks follow-up
(2) 12 months follow-up
(3) 16 weeks follow-up
(4) 12 month follow-up

Myers 1982 also reported cardiovascular mortality; in the 12 month follow-up period, two participants in the withdrawal group (n = 38) and one in the continuation group (n = 39) were reported to have died from cardiovascular causes (Analysis 1.2; very low certainty of evidence). One in each group died from heart failure and the second participant in the withdrawal group had a stroke (normal BP).

Myocardial infarction

Two studies reported the outcome of myocardial infarctions (MIs); Maland 1983 had a 12-month follow-up and Moonen 2015 had a 16-week follow-up. Both were included in the meta-analysis which found no evidence of a difference between the groups (OR = 1.86, 95% CI = 0.19 to 17.98, I² = 0%; Analysis 1.3). The certainty of the evidence was very low.

Adverse drug reactions and adverse drug withdrawal reactions

Meta-analysis for this outcome was not possible due to a large variation in how this outcome was reported between studies. Maland 1983 reported that there was no difference between groups in frequency of side effects or well-being although data for these outcomes was not shown. It was noted that in the continuation group (n = 31), one participant was removed from the study due to a complaint of sexual dysfunction and another for persistently elevated blood sugar. Reversal of a slight postural drop in SBP (observed at baseline in both groups) was reversed in the discontinuation group in the study by Myers 1982. Additionally, renal function and serum cholesterol levels improved (small but significant) in the discontinuation group (Myers 1982).

Three studies with participants taking mostly loop or thiazide-type diuretics reported change in potassium levels. Burr 1977 reported

that participants with low potassium at baseline had this reversed in the discontinuation group but not in the continuation group and Maland 1983 noted an increase in potassium in the discontinuation group. Myers 1982 reported that potassium increased in both groups (potassium supplementation was, however, prescribed at the discretion of the physician to both groups).

None of the studies reported whether or not any adverse drug withdrawal reactions occurred during the study period. However, Burr 1977 reported that the main clinical effect of withdrawal was increase in ankle oedema. In the discontinuation group (n = 41), 21 had an increase in oedema, 14 were unchanged and 6 had decreased levels with corresponding numbers in the continuation group (n = 48) of 14, 19 and 15. In most cases, the oedema increase was slight. Myers 1982, however, reported significant reductions in ankle oedema in both groups.

The certainty of the evidence for adverse drug reactions and adverse drug withdrawal reactions was determined to be very low due to very serious concern about lack of blinding, attrition bias and poor detection and reporting of outcomes and the small sample size and number of events.

Secondary outcomes

Blood pressure (BP)

Five studies (n = 767) were included in a meta-analysis of systolic blood pressure (SBP) (Burr 1977; Maland 1983; Moonen 2015; Myers 1982; Walma 1997). A mean difference of 9.75 mmHg (95% CI = 7.33 to 12.18) in favour of continuation compared to discontinuation was found (Figure 5 Analysis 1.4). The certainty of the evidence was low.

Figure 5. Forest plot of comparison: 1 Discontinuation by no treatment/placebo of antihypertensives vs Continuation, outcome: 1.4 Systolic blood pressure.

Study or Subgroup	Favours discontinuation			Continuation			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Burr 1977 (1)	136.3	12.7	41	131.8	12	48	22.0%	4.50 [-0.66 , 9.66]	
Maland 1983 (2)	143.2	23.45548976252679	31	122.8	19.79898987322333	31	5.0%	20.40 [9.59 , 31.21]	
Moonen 2015 (3)	5.4	21.46625258399792	180	-2	19.8997487421324	176	31.7%	7.40 [3.10 , 11.70]	
Myers 1982 (4)	135	23.45548976252679	26	125.3	19.79898987322333	32	4.6%	9.70 [-1.63 , 21.03]	
Walma 1997 (5)	8.8	17.31	102	-4.7	11.0875	100	36.6%	13.50 [9.50 , 17.50]	
Total (95% CI)			**380**			**387**	**100.0%**	**9.75 [7.33 , 12.18]**	

Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 7.89 (P < 0.00001)
Test for subgroup differences: Not applicable

Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 12 months follow-up, SD imputed
(3) 16 weeks follow-up
(4) 12 months follow-up
(5) 6 months follow-up

Substantial heterogeneity (I² = 67%) was observed in the SBP meta-analysis and, therefore, subgroup analyses by duration of use and class of medication were conducted according to prespecified plans. Three studies had a follow-up of less than 12 months (up to 12 weeks (Burr 1977), 16 weeks (Moonen 2015) and six months (Walma 1997)), and two had a follow-up of 12 months (Maland 1983; Myers 1982). This subgroup analysis was not able to explain the heterogeneity, and there were no significant differences between the mean differences in the two subgroups (Analysis 1.10; duration of follow-up < 12 months: mean difference = 9.17 mmHg, 95% CI = 6.62 to 11.71; duration of follow-up ≥ 12 months: mean difference = 15.30 mmHg, 95% CI = 7.48 to 23.12, P = 0.14). Subgroup analysis by drug class (diuretics (Burr 1977; Maland 1983; Myers 1982; Walma 1997) versus other (Moonen 2015)) was also not able to explain the heterogeneity and there was no difference between subgroups (Analysis 1.11).

The same five studies (n = 768) were also included in a meta-analysis of change in diastolic blood pressure (DBP) (Burr 1977; Maland 1983; Moonen 2015; Myers 1982; Walma 1997). A mean difference of 3.50 mmHg (95% CI = 1.82 to 5.18) was found in favour of continuation (Analysis 1.5) with a low certainty of evidence. Moderate heterogeneity was found (I² = 47%) and so subgroup analysis by duration of follow-up and drug class was conducted. The heterogeneity in the DBP analysis might be explained by duration of follow-up. The subgroup of < 12 months duration of follow-up had no heterogeneity, although heterogeneity remained in the studies with ≥ 12 months duration (Figure 6, Analysis 1.12). There was a significant difference between the studies with a follow-up of < 12 months compared to ≥ 12 months (mean difference = 2.68 mmHg, 95% CI = 0.87 to 4.49 and mean difference = 8.70 mmHg, 95% CI = 4.15 to 13.25 respectively, P = 0.02). Subgroup analysis by type of antihypertensive drug didn't explain the heterogeneity and there was no significant difference between these subgroups (Analysis 1.13).

Figure 6.   Forest plot of comparison: 1 Discontinuation by no treatment/placebo of antihypertensives vs Continuation, outcome: 1.12 Diastolic blood pressure sub grouped on duration of study.

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.12.1 Less than 12 months									
Burr 1977 (1)	82.4	8.3	41	81	9.6	47	20.2%	1.40 [-2.34 , 5.14]	
Moonen 2015 (2)	1.3	12.07476707849883	180	-1.3	10.61319932913728	176	50.6%	2.60 [0.24 , 4.96]	
Walma 1997 (3)	4.8	11.2006	102	0.2	18.6472	100	15.6%	4.60 [0.35 , 8.85]	
Subtotal (95% CI)			**323**			**323**	**86.4%**	**2.68 [0.87 , 4.49]**	

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)

1.12.2 12 months or longer									
Maland 1983 (4)	7.3	12.07476707849883	31	-2.6	10.61319932913728	31	8.8%	9.90 [4.24 , 15.56]	
Myers 1982 (5)	76	15.8745	28	69.5	14.1421	32	4.8%	6.50 [-1.15 , 14.15]	
Subtotal (95% CI)			**59**			**63**	**13.6%**	**8.70 [4.15 , 13.25]**	

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.75 (P = 0.0002)

Total (95% CI)			**382**			**386**	**100.0%**	**3.50 [1.82 , 5.18]**	

Heterogeneity: Chi² = 7.53, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 4.09 (P < 0.0001)
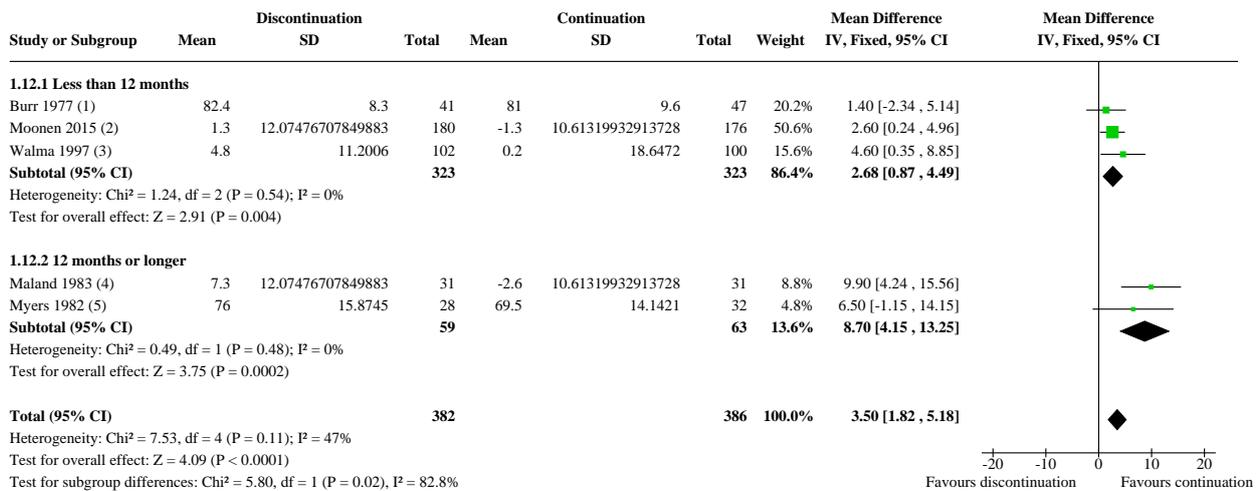Test for subgroup differences: Chi² = 5.80, df = 1 (P = 0.02), I² = 82.8%

-20 -10 0 10 20
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 16 weeks follow-up
(3) 6 months follow-up
(4) 12 months follow-up, SD imputed
(5) 12 months follow-up

Hospitalisation

Hospitalisation was reported as an outcome in a single study involving participants with mild cognitive defects (Moonen 2015). There were nine participants in the withdrawal group (n = 199) and 10 participants in the continuation group (n = 186) hospitalised during the 6-week follow-up (Analysis 1.6; OR = 0.83, 95% CI = 0.33 to 2.10). These results were noted to not include the participants who had died or experienced a vascular event. There was a low certainty of evidence due to serious concerns about the sample size and number of events.

Stroke (fatal and non-fatal, ischaemic and haemorrhagic, transient ischaemic attack)

Three studies with durations of 16 weeks to 12 months had stroke as an outcome (Maland 1983; Moonen 2015; Myers 1982) with a total of 524 participants included in a meta-analysis (Analysis 1.7). There was no evidence of a difference between discontinuation and continuation groups (OR = 1.44, 95% CI = 0.25 to 8.35). The certainty of the evidence was determined to be low due to serious concerns about indirectness and imprecision.

Success (rate) of withdrawal from antihypertensive drugs

Four studies reported the success of withdrawal as measured by the ability to remain off the medication. Three studies (Maland 1983; Myers 1982; Walma 1997; n = 341) were included in the meta-analysis which found an OR of 3.23 (95% CI 1.86 to 5.61, I² = 71.42%) in favour of continuation (Analysis 1.8). There was low certainty due to heterogeneity and indirectness.

Myers 1982 reported the number of participants that had to be withdrawn from the study due to clinically important hypertension (two consecutive readings above 180/110 mmHg) or heart failure in the 12-month follow-up period. Four out of 38 (10.5%) participants

in the discontinuation group were withdrawn (two for hypertension and two for heart failure) while six out of 39 (15.4%) participants in the continuation group were withdrawn (all due to heart failure). Maland 1983 also had a 12-month follow-up period and reported the number of participants who had to be restarted on their antihypertensive medication due to hypertension. The assessment was made using predefined criteria: average DBP ≥ 105 mmHg at any one visit, DBP 96 to 104 mmHg at any two visits, DBP > 90 mmHg at any five visits; or DBP > 90 mmHg at every visit in the first 24 weeks. Eight out of 31 (25.8%) and one out of 31 (3.2%) discontinuation and continuation participants were removed from the study due to hypertension, respectively. Participants in the discontinuation group who had to restart their medication due to hypertension were slightly older and had slightly higher blood pressure before treatment than those who didn't, however, the differences were not statistically significant. Walma 1997 was the largest study with this outcome, but had a shorter follow-up of 6 months and successful withdrawal from therapy was the primary outcome. Predefined criteria for re-initiation of diuretic therapy were heart failure (score of four or greater) or hypertension (an average of three measurements on separate occasions of SBP > 180 mmHg or DBP > 100 mmHg). In the discontinuation group, 34 (25 for heart failure, nine for hypertension) out of 102 (33.3%) required re-initiation of therapy and, in the continuation group, nine (four for heart failure and five for hypertension) out of 100 (9%) met the criteria. This study also reported that 16 and four participants in the discontinuation and continuation groups had their diuretic restarted by the doctor for other reasons (such as increased shortness of breath).

The study by Langford 1984 could not be included in the meta-analysis as no data on the outcome could be found for the continuation group. This study reported the percentage of participants in the discontinuation group who restarted the antihypertensive medication or had a terminating event (physician

outside of the study restarted the medication, stroke, new MI, heart failure or elevated creatinine level). The study criteria for restarting the medication was DBP 95 to 99 mmHg on three occasions within three months, DBP 100 to 104 mmHg on two occasions within one month or DBP ≥ 105 mmHg at any time. Langford 1984 reported that 35.3% and 45.0% in the obese and nonobese discontinuation groups (without dietary intervention) respectively remained withdrawn from their medication(s) after 56 weeks.

Quality of life (QoL)

One study (n = 356, participants with mild cognitive defects) reported change in quality of life (QoL) in the discontinuation and continuation groups using the Cantril Ladder (Moonen 2015) (single item scale, range from 1-10 with higher scores indicating better QoL). There was no significant difference in change in score after 16 weeks between the discontinuation and continuation groups (−0.09, 95% CI = −0.34 to 0.16; P = 0.46). It was determined that there was low certainty of evidence for this outcome due to risk of bias and small sample size (single study).

Falls

None of the included studies reported outcomes or data on the incidence, rate or risk of falls.

DISCUSSION

Summary of main results

Our systematic review identified six RCTs on antihypertensive discontinuation in older people. Based on currently available evidence, discontinuation of antihypertensives has no effect on all-cause mortality, MI, or stroke, compared with continuation; however, there is low or very low certainty in these results. Eligible studies were generally small and had short-term follow-up with few numbers of events. The meta-analysis results for these outcomes also had wide confidence intervals, which included both the null hypothesis (no difference) as well as an appreciable benefit in favour of continuation. Therefore, additional studies may change these results. We found no evidence that antihypertensive discontinuation increased the risk of adverse drug events, with some indication of a reversal of adverse drug reactions with discontinuation; however, eligible studies did not assess adverse drug *withdrawal* reactions specifically and, in general, all reporting of adverse drug events was very poor. It should be noted that the review and synthesis of adverse drug reactions and adverse drug withdrawal reactions did not include outcomes that were considered separately, for example, restarting of therapy due to increased BP or other clinical reasons. We did find evidence surrounding the effect of discontinuation on blood pressure and restarting of antihypertensives, however, again the certainty of evidence is low. Discontinuation led to an increase in both SBP and DBP compared to continuation, though there was heterogeneity in these estimates which could not be fully explained. Further, the proportion of persons withdrawing from studies due to worsening hypertension or heart failure (based on predefined criteria) leading to subsequent restarting of antihypertensive medications was higher in the discontinuation arm. Finally, we found that there was no effect of antihypertensive discontinuation on quality of life or hospitalisations (low certainty of evidence); however, these outcomes were only assessed in one study each.

Overall, the limited available evidence suggests that antihypertensive discontinuation in older people may have no effect on clinically-important outcomes such as mortality or cardiovascular events, with low certainty in this result. However, discontinuation may lead to an increase in blood pressure, requiring some patients to restart therapy. Between 10.5% and 33.3% of participants in the discontinuation group required restarting of therapy due to blood pressure or other clinical criteria compared to rates of 9% to 15% in the continuation group. A slightly higher rate of restarting (35.3% to 45.0%) was reported in one of the studies which didn't report the rate in the continuation group.

Overall completeness and applicability of evidence

There are a few factors which increase the applicability of the evidence to the population of interest, however, overall there is a lack of completeness and concern about the applicability of the evidence to the majority of older adults using antihypertensives for hypertension or primary prevention of CVD.

All included studies had inclusion criteria that mimic situations where discontinuation of the antihypertensive could be considered, that is, older adults with controlled blood pressure. However, there are other scenarios where discontinuation of antihypertensives would be considered that are not reflected in these studies, for instance, in situations where the individual has low BP, a postural drop in BP, or where they are potentially suffering from harm such as falls. Additionally, there was significant variability in the inclusion and exclusion criteria as to what they defined controlled blood pressure to be. For example, Walma 1997 excluded participants if their SBP was greater than 180 mmHg, while Moonen 2015 used a more conservative exclusion criteria of greater than 140 mmHg.

The conditions of RCTs limits the applicability of our findings. Specifically, in clinical practice, discontinuation of antihypertensive medications would be a result of shared decision-making, taking into account the values and preferences of the patient. Additionally, after discontinuation, blood pressure can be monitored and the medication would be restarted if the blood pressure rose above the acceptable level (for the individual). Additionally, only three (Langford 1984; Moonen 2015; Walma 1997) of the six studies reported tapering the dose of the medication prior to discontinuation and one only required tapering of beta-blockers and not other antihypertensives (Moonen 2015). Tapering would likely be conducted in clinical practice to determine the lowest effective dose of the medication (Reeve 2014b; Scott 2019). While the studies had criteria for definition of relapse of hypertension and study withdrawal, this was not consistent among the studies.

Another limitation to the applicability of the evidence is that five out of the six studies were conducted over 20 years ago. Standards of treatment, population risk factors (e.g. smoking) and recommendations about non-drug approaches have changed and there has been a reduction in cardiovascular mortality over this time period (Mensah 2017). There has also been an increase in the number of the oldest old, that is, those who are over 85 years old. These changes make it difficult to determine the applicability to the current population of older adults as the net treatment effect may have been altered over the intervening two decades. Similarly, over the past 20 years, there has been an increase in the prevalence of polypharmacy and this is now commonplace in older adults (Oktora 2019; Page 2019). None of the included studies reported

other medication use or noncardiovascular morbidity profiles of participants at baseline and so it is not possible to determine the applicability of the results to older adults with polypharmacy and multimorbidity. Additionally, no study measured or reported the frailty of participants. As frailty has recently been recognised as a key issue in relation to both the likely benefits and harms of antihypertensive use in older adults, ensuring assessment of frailty using validated tools is essential for future research in this area (Scott 2019).

Limited evidence was found for the majority of clinical outcomes. Cardiovascular mortality, hospitalisation, and quality of life were only reported in a single study each and none of the studies reported falls as an outcome. Several of the studies reported all-cause mortality and stroke, however, as the confidence intervals crossed both the null and a clinically important magnitude, we cannot make any firm conclusions about these outcomes. Additionally, there was little detail and apparently insufficient methods to capture adverse drug reactions and adverse drug withdrawal reactions.

Finally, four of the studies examined discontinuation of diuretics only and the remaining two included discontinuation of any antihypertensive medication. The results should be interpreted with caution for nondiuretic antihypertensive medications. We also did not identify any studies on the feasibility or outcomes of dose reduction of antihypertensives.

Quality of the evidence

The certainty of the evidence was judged to be low or very low for all the outcomes considered in this review. Therefore, there is uncertainty in the evidence of the effect of antihypertensive withdrawal on outcomes overall. The reasons for downgrading were risk of bias, inconsistency, indirectness, and imprecision.

While most studies were published prior to publication of the CONSORT statement (Moher 2009), they were identified to have methodological and reporting limitations. Only one RCT was assessed as having low risk of bias for all domains (Walma 1997). In four out of the six studies, there was insufficient information on the random sequence generation. The risk of bias from allocation concealment was judged as unclear in half of the studies. Two studies were judged as having a high level of potential performance bias due to lack of blinding of participants and personnel. Reporting on blinding of outcome assessment was judged as unclear or leading to high risk of bias in most studies. Two studies had high risk of bias for incomplete outcome data (high numbers and unbalanced dropouts). Selective reporting was judged to be unclear or leading to high risk of bias in five of the six included studies.

Potential biases in the review process

There are a number of limitations to our review process. Firstly, the importance of deprescribing and need to explore the benefits and harms is a relatively new concept. As such, data on the feasibility and outcomes in early studies were poorly reported. Additionally, while we used a variety of different search terms for deprescribing/withdrawal, it is possible that early studies reporting such results may not have used these terms and the search strategy we used has not been validated. Therefore, our search strategy may not have identified all relevant studies.

Few studies overall were included in this review; this is likely in part to result from our strict inclusion/exclusion criteria. It is important to consider that we excluded studies which included any additional intervention in either group, for example, dietary or exercise intervention in those that discontinued which would likely better reflect ideal practice. However, in older adults, the ability to conduct and adhere to such lifestyle interventions might be limited in real world practice. We also only included studies that withdrew all antihypertensive medications; the results of this review are not relevant to those taking multiple antihypertensives, where one is being considered for discontinuation.

We aimed to only include studies where the medication was used for hypertension or primary prevention of cardiovascular disease. However, many of the studies reported criteria for restarting that were related to heart failure. Therefore, it is possible that the populations in the studies did not truly satisfy our intended population.

Agreements and disagreements with other studies or reviews

This is the first systematic review and meta-analysis to investigate whether withdrawal of antihypertensive medications in older people with hypertension is feasible, and evaluate the effects of withdrawal on multiple outcome measures including mortality, cardiovascular outcomes, hypertension and quality of life. There have been a limited number of previous reviews which have aimed to assess the efficacy and safety of withdrawing antihypertensive medications in older people. Froom 1997 conducted a nonsystematic review of the effect of withdrawal of antihypertensive medications. In subgroup analysis of the six observational studies limited to older people, there was an average success rate of 26.2% for periods of two or more years, however, the authors did not report on specific outcome measures other than success of discontinuation. A systematic review by Iyer 2008 aimed to search for clinical studies of the benefits and harms of withdrawing a range of specific classes of medications in older people, not just antihypertensives. They included and reported on nine open-label, prospective observational studies of antihypertensive withdrawal in older people. No RCTs were included. Iyer 2008 reported that between 20% and 85% of participants did not recommence antihypertensive medications over a period of 4 to 260 weeks. No significant withdrawal syndromes were noted and the major reason for recommencing antihypertensive therapy was a gradual increase in blood pressure and, less commonly, heart failure. Similar reasons for restarting antihypertensive medications were identified in our review (blood pressure and heart failure), however, the proportion restarting in the discontinuation arms was generally lower in the RCTs included in our review (10.5% to 45.0%) than reported by Iyer 2008.

In another systematic review not limited to antihypertensives, Page 2016 aimed to determine whether deprescribing is feasible, and the impact on mortality and health outcomes in older adults. The review included a wider range of study designs; 132 randomised and nonrandomised studies across all settings and medication classes. The authors included 13 studies in the antihypertensive class (four RCTs, one case control, one historical cohort and seven before and after studies). Similar to the results of our review, they reported increases in systolic and diastolic BP, but no statistically significant difference in mortality.

Van der Wardt 2017 conducted a systematic review of withdrawal of antihypertensives to examine success and safety, however, this review was not limited to older adults or to RCTs. They included 66 articles and concluded that approximately one-quarter of people taking an antihypertensive could withdraw the medication without return of hypertension. Another systematic review not restricted to older adults concluded that patients with low BP, taking lower doses of antihypertensives, fewer number of antihypertensives and those motivated to implement lifestyle changes were more likely to remain normotensive after antihypertensive medication withdrawal (Nelson 2001).

A previous Cochrane review focused on the effect of withdrawal of antihypertensives on cognition (Jongstra 2016). They identified two studies (one of which was also included in our review (Moonen 2015)) and reported that, while there was a signal of a positive effect on cognition with withdrawal, there was too much uncertainty to make any strong conclusions. Previous nonRCT interventional studies have aimed to reduce the risk of falls through withdrawal of 'fall risk increasing drugs', which included antihypertensives. There have been conflicting results as to whether there is a benefit or not, however, this may have depended on how many and which medications were successfully withdrawn (Boye 2017; Van Der Velde 2007).

All these reviews conclude that deprescribing of antihypertensive medications (in those taking the medication for hypertensive or primary prevention of CVD) is likely feasible in a proportion of older adults, although the proportion in which it is likely to be successful varies. However, there is uncertainty in the likely benefit and harms of antihypertensive withdrawal.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review have clinical implications for the management of hypertension in older adults, and could be considered in the next updates of international guidelines. For example, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Whelton 2018) did not comment on withdrawal of antihypertensives beyond perioperative recommendations, although they do provide information on the risks of abrupt cessation of beta-blockers and clonidine (physiological adverse drug withdrawal reactions). The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines (Williams 2018) stated, 'Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, provided that treatment is well tolerated'. It also commented that 'it is well established that BP-lowering treatment withdrawal leads to a marked increase in CV disease', based on a subgroup analysis of the HYVET trial, which was designed to investigate treatment versus placebo rather than withdrawal of treatment. Our systematic review of deprescribing trials did not confirm this risk. Future iterations of treatment guidelines could consider also including data from deprescribing trials synthesised in our review.

The limitations of the available data on deprescribing of antihypertensives, as described in the discussion, restrict their impact on current practice. There is a paucity of high certainty evidence applicable to current practice and to the situations in which deprescribing is often considered clinically (frailty,

falls, dementia, polypharmacy), and an absence of data on key outcomes important to older adults, such as falls and quality of life. The variability in the populations and inclusion/exclusion criteria of the included studies mean that we can not make recommendations as to which individuals should have their antihypertensive medication deprescribed, or a BP cut-point at which deprescribing should occur. However, the feasibility of withdrawal and the lack of a significant increase in mortality, CVD or stroke in meta-analysis, may help clinicians when considering deprescribing antihypertensives and discussing this with patients, particularly in those who are at high risk of harm, such as those with frailty, falls, dementia and polypharmacy. Shared decision-making, specification of patient-specific goals (such as reversal of side effects or reduction of pill burden) and close monitoring of the effects in the individual remain pillars of clinical practice when deprescribing antihypertensives (Scott 2019).

Implications for research

The current state of evidence on antihypertensive discontinuation reveals several areas of focus for future research. More RCTs will help to further establish the potential benefit and safety of antihypertensive withdrawal, particularly in populations where there is uncertainty in the net benefit of treatment. Future RCTs would ideally be powered to detect differences in clinically meaningful outcomes such as cardiovascular events or mortality. These RCTs could also focus on evaluating the comparative effects of discontinuing different medication classes. For example, investigating whether there are differences in clinical outcomes, rates of withdrawal symptoms, and success rate between different medications or medication classes. Since the context for discontinuation may be different in certain populations (e.g. frail older person with multiple comorbidities versus low-risk younger old), it will also be helpful for future studies to examine whether differences in the potential benefit and safety of antihypertensive discontinuation exist between specific populations. It will also be useful for future studies to clearly describe their discontinuation plan (e.g. tapering rate and duration), such that discontinuation protocols can be replicated in other studies and/or more easily implemented in practice. Since risk of future cardiovascular events is of particular interest with respect to antihypertensive discontinuation, it will also be helpful for future studies to gather longer-term outcome data (12 months or beyond). This would serve to more clearly elucidate the downstream effects of antihypertensive discontinuation on cardiovascular events or mortality. Continuing to follow-up participants who have restarted the medication due to predefined BP or clinical criteria would provide important information for shared decision-making. Further, since return of underlying symptoms or adverse drug withdrawal events are also particularly relevant for antihypertensive discontinuation, future RCTs should include robust measures to capture this to provide a better picture of the safety of discontinuation. Finally, future studies should focus on evaluating patient-centred outcomes such as quality of life and falls.

In broader terms, this review highlights the need for more research into the benefits and harms of deprescribing specific medication classes to provide evidence to guide clinical decision-making and inform clinical practice guidelines. It will also be important to consider whether large RCTs are the best study design for this research question and the role of large observational database

studies to inform decision-making. Additionally, as identified in ours and previous reviews (Froom 1997; Iyer 2008), identifying deprescribing studies for systematic reviews can be challenging due to the wide variety of terminology in this space. Development of a standardised search strategy and recommendations for keyword referencing for all new studies in the field is likely to improve the ability to identify and synthesise evidence about deprescribing. The need for further research and synthesis of deprescribing research aligns with the internationally recognised problem of medical excess, such as overdiagnosis, overtreatment, and unnecessary testing (Johansson 2019).

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Burr 1977

Study characteristics	
Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group
Participants	**Number of participants randomised (discontinuation/continuation):** 54/52
	Baseline Characteristics
	Stop
	• *age of all; mean*: 81.6 years
	• *ethnicity*: not provided
	• *gender; % female (n)*: 87.0 (47)
	• *systolic blood pressure; mean (SD)*: 126.4 (15.2)
	• *diastolic blood pressure; mean (SD)*: 75.2 (10.3)

- *age of those who completed the trial; mean*: 80.5 years

Continue

- *age of all; mean*: 82.4 years
- *ethnicity*: not provided
- *gender; % female (n)*: 88.5 (46)
- *systolic blood pressure; mean (SD)*: 128.6 (15.3)
- *diastolic blood pressure; mean (SD)*: 78.2 (10.4)
- *age of those who completed the trial; mean*: 82.5 years

Overall

- *age of all; mean*: 82.0 years
- *ethnicity*: not provided
- *gender; % female (n)*: 87.7 (93)
- *systolic blood pressure; mean*: 127.6
- *diastolic blood pressure; mean*: 76.8
- *age of those who completed the trial; mean*: 81.6 years

Included criteria: On a long-stay geriatric ward. Prescribed a diuretic for more than 1 month. The consultant physicians agreed that there was no reason to believe that diuretic administration was mandatory.

Excluded criteria: If discontinuation of the treatment might be unsafe as defined by the following criteria: 1. They had had congestive cardiac failure during the previous three months; 2. They had ever had left ventricular failure; 3. They had hypertension which had been controlled in hospital by diuretic therapy; 4. They were receiving diuretics for a nephrotic syndrome or glaucoma.

Pretreatment: No detailed information on patient characteristics provided. Based on description in text and Table II, groups were balanced according to specific medication use and sex. But discontinuation group slightly younger (mean age 82.4 years for continuation versus 81.6 years for discontinuation group) and lower BP and heart rate at baseline

Withdrawal (from study) criteria: Death due to unrelated causes; diuretics considered necessary: congestive cardiac failure, left ventricular failure, increasing dyspnoea and oedema, tight calliper due to oedema, cellulitis of leg, oedema after leg injury, atrial fibrillation, bronchopneumonia; diuretics considered undesirable owing to difficulty in swallowing and dehydration

Process of drug withdrawal (tapering): Not specified

Antihypertensives taken: Frusemide, frusemide and spironolactone, amiloride-hydrocholorthiazide combination, frusemide and amiloride-hydrocholorthiazide combination, cyclopentiazide-potassium chloride combination, clopamide, chlorthalidone

Interventions	**Intervention Characteristics**
	Stop
	Continue

Outcomes	*Systolic blood pressure*
	- **Outcome type**: continuous outcome
	- **Unit of measure**: mmHg
	Diastolic blood pressure
	- **Outcome type**: continuous outcome
	- **Unit of measure**: mmHg
	Increase in oedema

Burr 1977 *(Continued)*

- **Outcome type**: dichotomous outcome

Decrease in oedema

- **Outcome type**: dichotomous outcome

Plasma potassium level

- **Outcome type**: continuous outcome
- **Unit of measure**: mEq/L

Urea level

- **Outcome type**: continuous outcome
- **Unit of measure**: mmol/L

Mortality

- **Outcome type**: dichotomous outcome

Identification	**Sponsorship source:** No sponsor listed. The following pharmaceutical manufacturers supplied the active and placebo tablets: CIBA Laboratories, Geigy Pharmaceuticals Ltd, Hoechst Pharmaceuti-cals Ltd, Merck Sharp & Dohme Ltd, Sandoz Products Ltd, and Searle Laboratories **Country:** Cardiff, Wales **Setting:** Long-stay geriatric wards (x 6) **Authors name:** M.L. Burr **Institution:** M.R.C. Epidemiology Unit, Cardiff, Gwent Geriatric Service, Newport and University Hospital of Wales, Cardiff **Email:** None provided **Address:** None provided
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... randomly allocated into two groups." Judgement comment: not enough information to make judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "... allocated into two groups." Judgement comment: not enough information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... tablets of similar appearance. Potassium supplements were similarly replaced by placebo tablets for patients allocated to the placebo group. The active and placebo tablets were supplied individually in special containers, so that the medical and nursing staff were unaware of the group to which each patient was assigned." Judgement comment: based on results in table IV, appeared that blinding was generally effective
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The patients were observed by the consultants or their deputies for signs of cardiac failure, especially during the first two weeks of the trial, so that diuretic therapy could be resumed if it was judged to be necessary. Plasma

Burr 1977 *(Continued)*

electrolyte estimations were performed before each patient entered the trial and repeated after four weeks and again after twelve weeks. Repeated observations of blood pressure, ankle oedema and general condition were made before and during the trial by the same nurse (S.K.)."

Judgement comment: not stated that assessors were blinded. As all observations done by same nurse, they would have seen BP results which could have biased their assessment of other factors

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The other 89 patients completed 12 weeks in the trial and are the subjects of the remaining tables." Judgement comment: results are reported only for those that completed the trial and not all enrolled. Table 3 shows uneven exclusions from the trial between active and placebo with higher dropout rate in placebo group and per protocol analysis.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: primary and secondary outcomes were not reported in the methods. A number of outcome results were reported but we weren't able to know if these were planned outcomes and if any were not reported. Most outcomes described in methods were reported in results; however, there was no detailed description for some outcomes.
Other bias	Low risk	Judgement comment: no other areas of concern

Langford 1984

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group
Participants	**Number of participants randomised (discontinuation/continuation):** 159/81 **Baseline Characteristics** Obese: continue (no dietary interventions) • *Age; mean* : 58.5 years • *Race, % black*: 75.0 • *Sex, % male*: 31.3 • *Systolic blood pressure; mean*: 131.2 • *Diastolic blood pressure; mean*: 79.6 Obese: discontinue medication (no dietary interventions) • *Age; mean* : 57.2 years • *Race, % black*: 69.7 • *Sex, % male*: 36.0 • *Systolic blood pressure; mean*: 127.6 • *Diastolic blood pressure; mean*: 79.6 Not obese: continue (no dietary interventions) • *Age; mean* : 58.1 years • *Race, % black*: 57.6 • *Sex, % male*: 48.5

Langford 1984 *(Continued)*

- *Systolic blood pressure; mean*: 126.2
- *Diastolic blood pressure; mean*: 80.0

Not obese: discontinue medication (no dietary interventions)

- *Age; mean* : 56.8 years
- *Race, % black*: 72.9
- *Sex, % male*: 50.0
- *Systolic blood pressure; mean*: 123.5
- *Diastolic blood pressure; mean*: 80.2

Included criteria: Participants were enrolled in the current programme (DISH: Dietary intervention Study of Hypertension) if they were previously active stepped care HDFP participants (at one of 3 centres (Jackson, Birmingham or NY)). Persons were eligible for participation in DISH if they: (1) had no systolic blood pressure > 180 mmHg recorded during the previous year; (2) the average of the diastolic blood pressure was < 95 mmHg during the past year; and (3) the average of the last two diastolic blood pressure readings was greater than or equal to 90 mmHg, and neither > 95 mmHg. Age 30-69. receiving antihypertensive for past 5 years, hypertension well controlled

Excluded criteria: Participants were excluded if they had a history of congestive heart failure, history or ECG evidence of myocardial infarction, history of stroke or transient ischaemic attacks, serum creatinine concentration > 2.5 mg/100 mL on at least two determinations, history of personal, social or psychological problems, or an intercurrent illness making compliance with the protocol dietary regimens difficult or impossible, or severe alcoholism, intercurrent pregnancy, beta-blocker therapy for angina, or glucocorticoid therapy for an indefinite period of time.

Pretreatment: There were modest examples of inhomogeneity of randomisation, as anticipated, with these relatively small groups. However, none of these were considered by study authors to be significant enough to affect analysis.

Withdrawal criteria (criteria for restarting medication): Medication was restarted if (a) the diastolic blood pressure reached 95 - 99 mmHg on three occasions within a three-month period; (b) if two diastolic blood pressures were in the 100 - 104 mmHg range during a one-month period; (c) if any time diastolic blood pressure rose to 105 mmHg or higher. If a participant's medication was restarted due to blood pressure rise as specified or if medication was restarted by physicians outside the study, this was considered a terminating event and the participant was counted as a withdrawal failure. Other occurrences defined as terminating events included stroke, new myocardial infarction, congestive heart failure, or elevated creatinine. Patients were considered a continuing success if medication had not been restarted for any of the above reasons and they had not had a terminating event at the time of analysis.

Group randomisation: Participants were initially grouped into those individuals who were 120% or more than ideal weight (obese) and those who weighed less (non-obese). The obese participants were randomised into four groups: (1) continue medication; (2) discontinue medication, no dietary intervention; (3) discontinue medication, weight loss; (4) discontinue medication, decrease sodium intake. The non-obese participants were randomised to three groups: (1) continue medication; (2) discontinue medications, no dietary intervention; (3) discontinue medication, sodium restriction.

Process of drug withdrawal (tapering): Participants randomised to discontinue drugs were withdrawn from therapy using a standardised step-down withdrawal programme taking from 2 to 8 weeks, depending on the number and dosage of drugs at entry. The diuretic was the last agent withdrawn. Drug withdrawal took place in a stepped fashion with the highest step drug being removed first. Target time for withdrawal was 6 weeks.

Antihypertensives taken: At the baseline visit, of the obese non-intervention group, 34% had their hypertension under control with diuretics alone (Hypertension Detection Follow-Up Program Step 1 drugs); another 37% were under control with diuretics plus either reserpine or methyldopa (Step 2); the remaining 29% were additionally on hydralazine (Step 3) and guanethedine (Step 4) and on other antihypertensive drugs (Step 5). Among those in the non-obese non-intervention group at baseline, 31% were on diuretics alone and another 29% were on diuretics plus reserpine or methyldopa. The remaining 40% were on Step 3, 4 or 5 drugs.

Interventions	**Intervention Characteristics**

Langford 1984 *(Continued)*

Obese: continue

Obese: discontinue medication (no dietary interventions)

Not obese: continue

Not obese: discontinue medication (no dietary interventions)

Outcomes	*Percentage remaining off antihypertensive medications* • **Outcome type**: dichotomous outcome
Identification	**Sponsorship source:** Grant R01 HL24369, with the National Heart, Lung and Blood Institute, NIH, Department of Health and Human Services. Drugs were supplied for this study by the following companies: Inderal, Ayerst Laboratories; Aldomet, Merck Sharp and Dohme; Apresoline and Ismelin, Ciba-Geigy Corp.; Catapres, Boehringer Ingelheim Ltd.; Hygroton and Rergoton, USV Pharmaceutical Corp.; Aldactone, Searle Laboratories **Country:** USA **Setting:** Primary care (community) **Authors name:** Herbert G. Langford **Institution:** Departments of Medicine, University of Mississippi Medical Center **Email:** None provided **Address:** Departments of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, US
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 584 eligible patients as shown in Fig 1 were stratified by clinical center and by obesity and randomized before requesting consent to one of the following seven groups..." Judgement comment: not enough information to make judgement
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not enough information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "... among these groups (Table 4); 23% of all failures were due to private (non- study) physicians' restarting therapy with antihypertensive medication, at least on some occasions despite continued normotension." Judgement comment: manuscripts did not specify if blinded. High possibility that they were not blinded (no mention of placebo tablets, plus, as there were dietary interventions in the other groups, this would not have been able to be blinded). Additionally, this quote would indicate that they weren't blinded. Outcomes were susceptible to bias due to participant and personnel lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: outcome of restarting antihypertensive medication was based on objective criteria related to BP readings though drug therapy could be restarted by physicians outside the study (private physician restart was reason for restart in around 25% of restarts in overweight group and 32% in

Langford 1984 *(Continued)*

		non-overweight). The decision to restart could be influenced by knowledge of group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: reported outcomes for participants in discontinuation groups, but not all outcomes in continuation group. No clear details on dropouts (particularly in continuation group)
Selective reporting (reporting bias)	High risk	Judgement comment: multiple papers published on this study, presenting results and different subgroup analyses which raises concern regarding selective reporting of results; based on methods in main paper, BP was measured at study visits though this does not appear to be reported.
Other bias	Low risk	Judgement comment: no other areas of concern

Maland 1983

Study characteristics	
Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group
Participants	**Number of participants randomised (discontinuation/continuation):** 31/31
	Baseline Characteristics
	Stop
	• *Sex, male n (%)*: 12 (38.71)
	• *Mean age*: 60.8 years
	• *Mean HDFP intake systolic BP (parent study), mmHg*: 154.2
	• *Mean HDFP intake diastolic BP (parent study), mmHg*: 99.3
	• *Mean pretrial systolic BP, mmHg*: 124.3
	• *Mean pretrial diastolic BP, mmHg*: 77.8
	Continue
	• *Sex, male n (%)*: 19 (61.29)
	• *Mean age*: 59.8 years
	• *Mean HDFP intake systolic BP (parent study), mmHg*: 152.3
	• *Mean HDFP intake diastolic BP (parent study), mmHg*: 99.2
	• *Mean pretrial systolic BP, mmHg*: 124.4
	• *Mean pretrial diastolic BP, mmHg*: 77.7
	Overall
	• *Sex, male n (%)*: 31 (50.0)
	• *Mean age*: 60.3 years
	• *Mean HDFP intake systolic BP (parent study), mmHg*: 153.2
	• *Mean HDFP intake diastolic BP (parent study), mmHg*: 99.2
	• *Mean pretrial systolic BP, mmHg*: 124.3
	• *Mean pretrial diastolic BP, mmHg*: 77.8
	Included criteria: An average DBP of 90 mmHg or less at an eligibility visit plus the two preceding visits. No DBP above 95 mm Hg at any of the above 3 visits. An average DBP of 90 mm Hg or less for all visits during the preceding 12 months. Only antihypertensive medication used during the preceding 12 months was a diuretic.

Maland 1983 *(Continued)*

Excluded criteria: History of major cardiovascular events, such as stroke, myocardial infarction, transient ischaemic attack, congestive heart failure, renal failure, and severe angina pectoris. Evidence by valid count of unused medication on more than two occasions during the preceding 12 months, of less than 80% or more than 110% of prescribed usage. Inability or unwillingness to attend clinic at least once every 4 to 6 weeks.

Pretreatment: The following characteristics were measured: gender, race, age, mean BP, mean pretrial BP, pre-HDFP (Hypertension Detection and Follow-up Program), history of hypertension, antihypertensive treatment at HDFP intake. Differences not explicitly stated in the text. As per Table 2, there were more males than females in active (continuation) versus placebo (stop) group; mean age similar in both groups. BP measures were similar across groups.

Removal criteria: Any one visit with an average DBP of 105 mmHg or higher; any 2 visits with an average DBP of 96-104 mmHg; any 5 visits with an average DBP above 90 mmHg; an average DBP above 90 mmHg for all visits at the end of the first 24 weeks

Process of drug withdrawal (tapering): Not specified

Antihypertensives taken: Of 62 enrolled subjects, 54 (87%) were taking chlorthalidone, 7 (11%) were taking hydrochlorothiazide, and 1 (2%) was taking triamterene. All pretrial regimens had been in use for at least 12 months of the HDFP. None of the participants in the trial was taking potassium supplement, uricosuric drugs, or allopurinol.

Interventions	**Intervention Characteristics** Stop Continue
Outcomes	*Reversions (restarted pretrial medication due to BP)* • **Outcome type**: dichotomous outcome *Systolic BP change (mean BP of last 2 trial visits minus pretrial BP)* • **Outcome type**: continuous outcome • **Data value**: change from baseline *Diastolic BP change (mean BP of last 2 trial visits minus pretrial BP)* • **Outcome type**: continuous outcome • **Data value**: change from baseline *Systolic BP* • **Outcome type**: continuous outcome *Mortality* • **Outcome type**: dichotomous outcome *Stroke (fatal and non-fatal, ischaemic and haemorrhagic, transient ischaemic attack)* • **Outcome type**: dichotomous outcome *MI* • **Outcome type**: dichotomous outcome
Identification	**Sponsorship source:** Supported in part by a grant from the Montana State Heart Association. The United States Vitamin Corporation and Abbott Laboratories generously supplied the active and placebo dosage forms used in this study. **Country:** USA

Maland 1983 *(Continued)*

Setting: Community setting

Comments: A follow-on study on a subset of participants from the National Hypertension Detection and Follow-up Program (HDFP) - those from the Salt Lake City Clinical Centre

Authors name: Lynn J. Maland

Institution: Department of Family and Community Medicine, University of Utah, Salt Lake City, Utah

Email: Not stated

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Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... were randomly assigned in a double-blind manner." Judgement comment: not enough information to make judgement
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not enough information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... double- blind manner to receive either the same diuretic they had been taking at the end of the HDFP, or a physically identical placebo." Judgement comment: noted to be 'double-blind', physically identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "... two each using a standard and a random zero mercury manometer (Hawksley, England) and an appropriately sized cuff. The random zero device conceals the true zero point of the mercury column until the reading is completed to avoid digit preferences in BP readings." "The average of the two random zero measurements (the 2nd and 4th) was taken as the official reading for each visit. The diastolic pressure was read as the 5th phase of the Korotkov sounds." Judgement comment: the study was said to be 'double-blind' but no further information. This method was intended to remove digit bias in assessors, but not necessarily related to blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty-nine of the original 62 enrollees completed the 1-year follow-up. The three who did not complete the study included one patient in the active treatment group who died from cardiac arrest, and two dropouts from the placebo group." Judgement comment: small total number of dropouts - different reasons for dropout between groups, but as such small number unable to determine if due to treatment. One in each group had a cardiac event which led to their dropout (one due to death).
Selective reporting (reporting bias)	High risk	Judgement comment: all stated outcomes in the methods were reported - but the manner in which they were reported was unclear. BP results were given with reverters as a separate group (i.e. not randomised group). Adverse drug reactions mentioned but full details not given. Also unclear whether other outcomes not mentioned in the manuscript

Maland 1983 *(Continued)*

Other bias	Low risk	Judgement comment: no other areas of concern

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Moonen 2015

Study characteristics

Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group

Participants	**Number of participants randomised (discontinuation/continuation):** 199/186
	Baseline Characteristics
	Stop
	• *Sex, male n (%)*: 77 (42.8)
	• *Mean age (SD)*: 81.1 (4.3) years
	• *SBP, mean (SD), mmHg*: 148.8 (21.1)
	• *DBP, mean (SD), mmHg*: 82.3 (10.8)
	• *Orthostatic HTN, n (%)*: 86 (47.8)
	• *MMSE, median (IQR)*: 26 (25-27)
	Continue
	• *Sex, male n (%)*: 70 (39.8)
	• *Mean age (SD)*: 81.5 (4.6) years
	• *SBP, mean (SD), mmHg*: 147.0 (22.3)
	• *DBP, mean (SD), mmHg*: 80.0 (10.7)
	• *Orthostatic HTN, n (%)*: 77 (43.8)
	• *MMSE, median (IQR)*: 26 (25-27)
	Overall
	• *Sex, male n (%)*: not reported
	• *Mean age (SD)*: not reported
	• *SBP, mean (SD), mmHg*: not reported
	• *DBP, mean (SD), mmHg*: not reported
	• *Orthostatic HTN, n (%)*: not reported
	• *MMSE, median (IQR)*: not reported
	Included criteria: 75 years or older, used antihypertensive treatment, systolic BP of 160 mmHg or less, and a Mini-Mental State Examination (MMSE) score of 21 to 27. Persons with a history of peripheral arterial disease, myocardial infarction, or a coronary reperfusion procedure or persons with diabetes mellitus could participate if their SBP was 140 mmHg or less.
	Excluded criteria: A clinical diagnosis of dementia, use of antihypertensives for reasons other than hypertension, current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure less than 3 years ago, a history of stroke or transient ischaemic attack, a limited life expectancy
	Pretreatment: Baseline characteristics of both groups were well balanced except for a slight imbalance in the use of β-blockers and in Trail Making Test Δ scores.
	Removal criteria: During the 6-16-week period after randomisation, the physician was instructed to restart antihypertensive treatment for safety reasons when measurements of BP at the home visit showed a diastolic BP of 120 mmHg or greater, an SBP of 200 mmHg or greater (180 mmHg for partici-

pants with diabetes mellitus or those who had a cardiovascular event > 3 years ago), or an increase in SBP of 60 mmHg or greater relative to baseline.

Antihypertensives taken: Intervention (discontinuation)/Control (continuation): β-Blocker 64 (35.6)/75 (42.6); diuretic 99 (55.0)/92 (52.3); angiotensin-converting enzyme inhibitor 60 (33.3)/61 (34.7); angiotensin receptor blocker 60 (33.3)/63 (35.8); calcium channel blocker 40 (22.2)/40 (22.7); ≥ 2 agents 109 (60.6)/110 (62.5)

Process of withdrawal: The discontinuation of antihypertensive treatment was performed by the participant's physician according to an algorithm composed by the investigators (outlined in Supplement 2). All physicians were instructed to withdraw antihypertensive treatment until a maximum increase of 20 mmHg in SBP was reached. During this phase, the physician monitored BP every week until no further changes in antihypertensive treatment were made.

Interventions	**Intervention Characteristics** Stop Continue
Outcomes	*Systolic BP change (ITT)* • **Outcome type**: continuous outcome • **Data value**: change from baseline *Diastolic BP change (ITT)* • **Outcome type**: continuous outcome • **Data value**: change from baseline *Mortality* • **Outcome type**: dichotomous outcome *Stroke* • **Outcome type**: dichotomous outcome *MI* • **Outcome type**: dichotomous outcome *QOL* • **Outcome type**: continuous outcome • **Data value**: change from baseline *TIA* • **Outcome type**: dichotomous outcome *Hospitalisations (total)* • **Outcome type**: dichotomous outcome
Identification	**Sponsorship source:** This work was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw), Program Priority Medicines for the Elderly (grant no: 40-41600-98-9014). This funding source had no role in the study design, the collection, analysis and interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication. All researchers worked independently from the funding source. **Country:** Netherlands **Setting:** Community-based; across 128 general practices

Moonen 2015 *(Continued)*

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Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned, in a 1:1 ratio, to parallel discontinuation (intervention group) or continuation (control group) of antihypertensive treatment (Figure 1). Stratified block randomization was used (with block sizes of 4 per general practice) to ensure that intervention and control participants were equally distributed within general practices." Judgement comment: a computerised randomisation procedure was used.
Allocation concealment (selection bias)	Low risk	Quote: "Concealment of treatment allocation was ensured by a central computerized randomization procedure." Judgement comment: concealment of treatment allocation was ensured by a central computerised randomisation procedure.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and the physicians conducting the intervention were not masked to the allocated intervention." Judgement comment: participants and the physicians conducting the intervention were not blinded. Many of the outcomes (or reporting of outcomes) may have been susceptible to bias due to knowledge of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study outcomes and MRIs were assessed in a standardized manner by research personnel ... masked to the allocated intervention." Judgement comment: paper stated that study outcomes and MRIs were assessed in a standardised manner by research personnel masked to the allocated intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Furthermore, 19 participants in the intervention group and 10 in the control group had no follow-up measurement." Judgement comment: a per-protocol analysis was performed. Reason for missing data was unlikely to be related to the true outcome of this study.
Selective reporting (reporting bias)	High risk	Judgement comment: study protocol (provided as supplementary material) noted that Neuropsychiatric Inventory (NPI) would be carried out for, among others, assessment of depression and apathy. This outcome was not reported.
Other bias	Low risk	Judgement comment: no other areas of concern

Myers 1982

Study characteristics

Myers 1982 *(Continued)*

Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group
	Stratification of randomisation: The randomisation process included stratification for the presence of heart disease and/or hypertension. Study was double-blind.
Participants	**Number of participants randomised (discontinuation/continuation):** 38/39
	Baseline Characteristics
	Stop (placebo)
	• *Male gender, n (%)*: 29 (76.3)
	• *With previous hypertension, n (%)*: 9 (23.7)
	• *With previous CHF, n (%)*: 5 (13.2)
	• *With both hypertension and CHF, n (%)*: 5 (13.2)
	• *age of males, mean*: 80.9 years
	• *age of females, mean*: 84.2 years
	Continue
	• *Male gender, n (%)*: 31 (79.5)
	• *With previous hypertension, n (%)*: 10 (25.6)
	• *With previous CHF, n (%)*: 4 (10.3)
	• *With both hypertension and CHF, n (%)*: 4 (10.3)
	• *age of males, mean*: 79.1 years
	• *age of females, mean*: 84.5 years
	Overall
	• *Male gender, n (%)*: 60 (77.9)
	• *With previous hypertension, n (%)*: 19 (24.7)
	• *With previous CHF, n (%)*: 9 (11.7)
	• *With both hypertension and CHF, n (%)*: 9 (11.7)
	• *age of males, mean*: 80.0 years
	• *age of females, mean*: 84.4 years
	Included criteria: Resident of geriatric institution. Taking one or more diuretics (hydrochlorothiazide, frusemide, spironolactone, hydrochlorothiazide and spironolactone, hydrochlorothiazide and tri-amterene). 60 years and over
	Excluded criteria: Concurrent digoxin use; individuals with clinical or radiological evidence of heart failure; residents with hypertension (blood pressure requiring nondiuretic antihypertensive therapy or a level above 160 mmHg systolic and/or 105 mmHg diastolic while receiving diuretics); on diuretic therapy less than 3 months; uncooperative/no consent; terminal illness unrelated to diuretic.
	Pretreatment: The mean daily dose of diuretic was slightly higher in the diuretic group at baseline but this difference was not present at 12 months. Mean baseline blood pressures in the supine position were similar in the two groups. Sitting and erect values were slightly higher in the placebo subjects, whereas initial postural blood pressure changes were more marked in the diuretic group. The mean heart rates of the two groups were similar.
	Withdrawal criteria: Heart failure or clinically significant hypertension: the presence or absence of heart failure was determined by the physician according to criteria used in the Framingham Study. Clinically important hypertension was defined as a blood pressure above 180 mmHg systolic and 110 mmHg diastolic on two consecutive visits at least one week apart.
	Process of drug withdrawal (tapering): Not specified

Myers 1982 *(Continued)*

	Antihypertensives taken: hydrochlorothiazide - 18/14 (continue/stop); frusemide - 17/20; spironolactone - 4/0; hydrochlorothiazide and spironolactone - 5/2; hydrochlorothiazide and triamterene - 3/4
Interventions	**Intervention Characteristics**
	Stop (placebo)
	Continue
Outcomes	*Systolic blood pressure (sitting)*
	• **Outcome type**: continuous outcome
	Diastolic BP (sitting)
	• **Outcome type**: continuous outcome
	Stroke fatal
	• **Outcome type**: dichotomous outcome
	Stroke fatal and non-fatal
	• **Outcome type**: dichotomous outcome
	Mortality (all-cause)
	• **Outcome type**: dichotomous outcome
	Cardiovascular mortality
	• **Outcome type**: dichotomous outcome
	Fatal and non-fatal cardiovascular events (heart failure, hypertension, stroke)
	• **Outcome type**: dichotomous outcome
	Withdrawal due to hypertension
	• **Outcome type**: dichotomous outcome
	Withdrawal for any reason
	• **Outcome type**: dichotomous outcome
Identification	**Sponsorship source:** Ontario Heart Foundation
	Country: Canada
	Setting: Two geriatric institutions
	Authors name: Martin G. Myers
	Institution: Sunnybrook Hospital
	Email: martin.myers@sunnybrook.ca
	Address: 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Myers 1982 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly allocated to either continued diuretic therapy or placebo".
		Quote: "The randomization process included stratification for the presence of heart disease and/or hypertension."
		Judgement comment: not enough information to make judgement
Allocation concealment (selection bias)	Low risk	Quote: "... randomization code was kept in the Department of Pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind design." "Matching placebo tablets were available for each diuretic, Slow K and potassium chloride solution. The potassium chloride solution did not have the same taste as the active compound otherwise the placebo and active tablets were identical. None of the three subjects on placebo potassium chloride commented on a change in therapy during the study."
		Judgement comment: noted to be double blind. While possibility that participants could taste a difference, none commented so likely low risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: not enough information to make judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: uneven dropouts with reasons for dropout uneven. Overall large number of dropouts/incomplete data for main outcome of BP
Selective reporting (reporting bias)	Unclear risk	Judgement comment: there was no protocol available, not enough information to make judgement
Other bias	Low risk	Judgement comment: no other areas of concern

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Walma 1997

Study characteristics	
Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group
Participants	**Number of participants randomised (discontinuation/continuation):** 102/100
	Baseline characteristics
	Stop
	• *Age; mean (SE)*: 76 (1) years
	• *Women; n (%)*: 81 (79.4%)
	• *Systolic blood pressure; mean (SE)*: 147 (2)
	• *Diastolic blood pressure; mean (SE)*: 81 (1)
	• *Duration of diuretic therapy mean (SE)* : 7.2 (0.5)
	Continue
	• *Age; mean (SE)*: 76 (1) years
	• *Women; n (%)*: 70 (70.0%)

Walma 1997 *(Continued)*

- *Systolic blood pressure; mean (SE)*: 147 (2)
- *Diastolic blood pressure; mean (SE)*: 81 (1)
- *Duration of diuretic therapy mean (SE)* : 7.6 (0.6)

Included criteria: patients aged 65 or more who had been receiving diuretics for at least six months and had no overt heart failure or hypertension

Excluded criteria: history of acute heart failure, defined as admission to hospital or prescription of intravenous diuretic therapy; symptoms of heart failure during the previous three months; manifest heart failure, defined as a heart failure score of over 4; use of frusemide at dosages over 80 mg/day; mean of three blood pressure values (two measured at successive home visits and one obtained from the medical file) > 180/100 mm Hg; hypercalciuria, nephrotic syndrome, and glaucoma; use of fixed combinations of diuretics with,blockers or angiotensin converting enzyme inhibitors; combination therapy of beta-blockers, diuretics, and vasodilators for hypertension; use of a diuretic for which no placebo was available; and non-compliance during the run in phase. In addition, 57 patients or their general practitioners refused to cooperate and seven eligible patients could not be enrolled in the trial for logistic reasons.

Pretreatment: The two groups were similar in all relevant baseline characteristics, including age, gender, current indication for diuretic therapy, heart failure score, New York Heart Association classification, SBP, DBP.

Withdrawal criteria: Patients with frusemide dosages of 40 or 80 mg/day went through a dose-halving regimen of one and two weeks, respectively, to prevent severe rebound effects. Dose halving was started immediately after randomisation and was performed double-blind.

Process of drug withdrawal (tapering): Participants with frusemide dosages of 40 or 80 mg/day went through a dose-halving regimen of one and two weeks, respectively, to prevent severe rebound effects. Dose halving was started immediately after randomisation and was performed double-blind.

Antihypertensives taken: frusemide (including combinations with other diuretics), thiazide (including combinations with other diuretics), triamterene monotherapy

Interventions	**Intervention Characteristics** Stop Continue
Outcomes	*Systolic blood pressure* - **Outcome type**: continuous outcome *Diastolic blood pressure* - **Outcome type**: continuous outcome *Withdrawal for any reason* - **Outcome type**: dichotomous outcome *Withdrawal due to heart failure* - **Outcome type**: dichotomous outcome *Withdrawal due to hypertension* - **Outcome type**: dichotomous outcome
Identification	**Sponsorship source:** Dutch Organisation for Scientific Research (NWO, Research Grant number 920≠01≠173) **Country:** Netherlands

Walma 1997 *(Continued)*

Setting: Participants from eight general practices

Authors name: Edmond P Walma

Institution: Erasmus University Medical School, Rotterdam

Email: walma@hag.fgg.eur.n

Address: Department of General Practice, Erasmus University Medical School, PO Box 1738, 3000 DR Rotterdam, Netherlands

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... each patient was randomly assigned to placebo (the withdrawal group) or continuation of diuretic therapy (the control group), after stratification by age (65-79 and > 80 years) and type of diuretic. Blocks of four sets of study medication each consisted of two placebo and two genuine packages, which were consecutively assigned to enrolled patients."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation lists and numbered sets of study medication were generated by the trial pharmacist of the Academic Hospital, who also produced sealed envelopes with decoding information for emergencies."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The similarity of genuine and placebo tablets ensured the possibility of recognising them by colour, form, or taste. The randomisation list remained in the pharmacy of the Academic Hospital in Rotterdam, separate from the trial centre in Schoonhoven. Of the sealed envelopes one copy was kept in the trial centre and another with the patient at home (for emergencies)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The codes were broken either after the assessment of the last set of data, or when a diuretic prescription was needed, in which case the primary outcome of the study became actual."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: outcome recorded on all patients in the study
Selective reporting (reporting bias)	Low risk	Quote: "The primary outcome variable was successful withdrawal from diuretic therapy. Patients in the withdrawal group who were still taking blinded study medication at the end of the six month follow-up period were considered successfully withdrawn. Those patients who met one of the predefined criteria for requiring diuretic therapy within the follow-up period were considered to be unsuccessfully withdrawn. Criteria for prescription of diuretic therapy were: (a) heart failure score exceeding 4 points or (b) a mean of three duplicate systolic or diastolic blood pressure measurements on separate occasions of > 180 mm Hg or > 100 mm Hg, respectively. Further, patients in whom diuretic therapy was restarted by their doctor for other reasons — for example, symptoms of increased shortness of breath — were considered to be unsuccessfully withdrawn. Changes in systolic and diastolic blood pressures are presented as secondary outcomes."
Other bias	Low risk	Judgement comment: no other areas of concern

BP: Blood pressure
CHF: Congestive heart failure

DISH: Dietary intervention study of hypertension
DBP: Diastolic blood pressure
ECG: Electrocardiogram
HDFP: Hypertension detection and follow-up program
HTN: Hypertension
IQR: Interquartile range
ITT: Intention to treat
MI: Myocardial infarction
MMSE: Mini-Mental State Examination
NPI: Neuropsychiatric Inventory
QOL: Quality of life
SBP: Systolic blood pressure
SE: Standard error
TIA: Transient ischaemic attack

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

Study	Reason for exclusion
Aberg 1989	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Andersen 2008	Wrong patient population
Andersen 2009	Wrong patient population
Blaufox 1984	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Blom 1993	Wrong intervention
Boye 2017	Wrong intervention
Burt 2017	Protocol paper (of an ineligible study due to wrong intervention)
Ekbom 1992	Wrong study design
ENOS Trial Investigators 2015	Wrong intervention
Gulla 2018	Wrong intervention
Guthrie 2002	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Hansen 1983	Wrong study design
He 2018	Wrong intervention
Jondeau 2009	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Kostis 1998	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Langford 1985	Wrong patient population

Study	Reason for exclusion
Lewin 2012	Wrong patient population
Luymes 2018	Wrong patient population
Manning 2015	Wrong intervention
Medical Research Council Working Party 1986	Wrong patient population
NCT00219063 2005	Wrong patient population
NCT00785512 2008	Clinical trial registry citation (of an ineligible study due to wrong patient population)
Nelson 2003	Wrong study design
Neusy 1989	Wrong intervention
NHF 1981	Wrong intervention
Ponten 1982	Wrong intervention
Popa 1995	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Robinson 2010	Wrong intervention
Ruoff 1986	Wrong population as not older adults; half of participants < 50 years
Szam 1981	Wrong study design
Vaur 1998	Wrong intervention
Veterans Administration Cooperative 1975	Wrong patient population
Xu 2017	Wrong intervention

DATA AND ANALYSES

Comparison 1. Discontinuation by no treatment/placebo of antihypertensives vs Continuation

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.1 All-cause mortality	4	630	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [0.79, 5.46]
1.2 Cardiovascular mortality	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.21, 20.19]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3 Myocardial infarction (fatal and nonfa-tal)	2	447	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.86 [0.19, 17.98]
1.4 Systolic blood pressure	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.5 Diastolic blood pressure	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.6 Hospitalisation	1	385	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.33, 2.10]
1.7 Stroke (fatal + nonfatal + TIA)	3	524	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.25, 8.35]
1.8 Sucess rate - withdrawal/resumption due to hypertension or other clinical rea-son	3	341	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.23 [1.86, 5.61]
1.9 Quality of life	1	356	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.35, 0.15]
1.10 Systolic blood pressure subgrouped on duration	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.10.1 Less than 12 months	3	647	Mean Difference (IV, Fixed, 95% CI)	9.17 [6.62, 11.71]
1.10.2 12 months or longer	2	120	Mean Difference (IV, Fixed, 95% CI)	15.30 [7.48, 23.12]
1.11 Systolic blood pressure subgrouped on drug type	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.11.1 Diuretics	4	411	Mean Difference (IV, Fixed, 95% CI)	10.85 [7.92, 13.78]
1.11.2 Other	1	356	Mean Difference (IV, Fixed, 95% CI)	7.40 [3.10, 11.70]
1.12 Diastolic blood pressure subgrouped on duration	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.12.1 Less than 12 months	3	646	Mean Difference (IV, Fixed, 95% CI)	2.68 [0.87, 4.49]
1.12.2 12 months or longer	2	122	Mean Difference (IV, Fixed, 95% CI)	8.70 [4.15, 13.25]
1.13 Diastolic blood pressure subgrouped on drug type	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.13.1 Diuretics	4	412	Mean Difference (IV, Fixed, 95% CI)	4.42 [2.03, 6.81]
1.13.2 Other	1	356	Mean Difference (IV, Fixed, 95% CI)	2.60 [0.24, 4.96]

Analysis 1.1. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 1: All-cause mortality

Study or Subgroup	Favours discontiuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Burr 1977 (1)	3	54	1	52	23.6%	2.69 [0.37 , 19.68]	
Maland 1983 (2)	0	31	1	31	6.1%	0.14 [0.00 , 6.82]	
Moonen 2015 (3)	1	199	1	186	12.1%	0.93 [0.06 , 15.02]	
Myers 1982 (4)	8	38	3	39	58.1%	2.94 [0.83 , 10.44]	
Total (95% CI)		**322**		**308**	**100.0%**	**2.08 [0.79 , 5.46]**	
Total events:	12		6				

Heterogeneity: Chi² = 2.53, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable

0.001　0.1　1　10　1000
Favours discontiuation　Favours continuation

Footnotes
(1) 12 weeks follow-up
(2) 12 months follow-up
(3) 16 weeks follow-up
(4) 12 month follow-up

Analysis 1.2. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 2: Cardiovascular mortality

Study or Subgroup	Discontinuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Myers 1982	2	38	1	39	100.0%	2.04 [0.21 , 20.19]	
Total (95% CI)		**38**		**39**	**100.0%**	**2.04 [0.21 , 20.19]**	
Total events:	2		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

0.01　0.1　1　10　100
Favours discontinuation　Favours continuation

Analysis 1.3. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 3: Myocardial infarction (fatal and nonfatal)

Study or Subgroup	Discontinuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Maland 1983 (1)	1	31	0	31	33.4%	7.39 [0.15 , 372.38]	
Moonen 2015 (2)	1	199	1	186	66.6%	0.93 [0.06 , 15.02]	
Total (95% CI)		**230**		**217**	**100.0%**	**1.86 [0.19 , 17.98]**	
Total events:	2		1				

Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

0.01　0.1　1　10　100
Favours discontinuation　Favours continuation

Footnotes
(1) Follow up at 12-months
(2) Follow-up at 16 weeks

Analysis 1.4. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 4: Systolic blood pressure

Study or Subgroup	Favours discontinuation			Continuation			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Burr 1977 (1)	136.3	12.7	41	131.8	12	48	22.0%	4.50 [-0.66 , 9.66]	
Maland 1983 (2)	143.2	23.45548976252679	31	122.8	19.79898987322333	31	5.0%	20.40 [9.59 , 31.21]	
Moonen 2015 (3)	5.4	21.46625258399792	180	-2	19.8997487421324	176	31.7%	7.40 [3.10 , 11.70]	
Myers 1982 (4)	135	23.45548976252679	26	125.3	19.79898987322333	32	4.6%	9.70 [-1.63 , 21.03]	
Walma 1997 (5)	8.8	17.31	102	-4.7	11.0875	100	36.6%	13.50 [9.50 , 17.50]	
Total (95% CI)			**380**			**387**	**100.0%**	**9.75 [7.33 , 12.18]**	

Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 7.89 (P < 0.00001)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 12 months follow-up, SD imputed
(3) 16 weeks follow-up
(4) 12 months follow-up
(5) 6 months follow-up

Analysis 1.5. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 5: Diastolic blood pressure

Study or Subgroup	Discontinuation			Continuation			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Burr 1977 (1)	82.4	8.3	41	81	9.6	47	20.2%	1.40 [-2.34 , 5.14]	
Maland 1983 (2)	7.3	12.07476707849883	31	-2.6	10.61319932913728	31	8.8%	9.90 [4.24 , 15.56]	
Moonen 2015 (3)	1.3	12.07476707849883	180	-1.3	10.61319932913728	176	50.6%	2.60 [0.24 , 4.96]	
Myers 1982 (4)	76	15.8745	28	69.5	14.1421	32	4.8%	6.50 [-1.15 , 14.15]	
Walma 1997 (5)	4.8	11.2006	102	0.2	18.6472	100	15.6%	4.60 [0.35 , 8.85]	
Total (95% CI)			**382**			**386**	**100.0%**	**3.50 [1.82 , 5.18]**	

Heterogeneity: Chi² = 7.53, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable

-20 -10 0 10 20
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 12 months follow-up, SD imputed
(3) 16 weeks follow-up
(4) 12 months follow-up
(5) 6 months follow-up

Analysis 1.6. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 6: Hospitalisation

Study or Subgroup	Discontinuation		Continuation		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
	Events	Total	Events	Total			
Moonen 2015 (1)	9	199	10	186	100.0%	0.83 [0.33 , 2.10]	
Total (95% CI)		**199**		**186**	**100.0%**	**0.83 [0.33 , 2.10]**	
Total events:	9		10				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours discontinuation   Favours continuation

Footnotes
(1) 16 weeks follow-up

Analysis 1.7. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 7: Stroke (fatal + nonfatal + TIA)

Study or Subgroup	Discontinuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Maland 1983 (1)	0	31	1	31	20.1%	0.14 [0.00 , 6.82]	
Moonen 2015 (2)	2	199	1	186	59.8%	1.83 [0.19 , 17.70]	
Myers 1982 (1)	1	38	0	39	20.1%	7.59 [0.15 , 382.44]	
Total (95% CI)		**268**		**256**	**100.0%**	**1.44 [0.25 , 8.35]**	
Total events:	3		2				

Heterogeneity: Chi² = 2.13, df = 2 (P = 0.34); I² = 6%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours discontinuation — Favours continuation

Footnotes
(1) 12 months follow-up
(2) 16 weeks follow-up

Analysis 1.8. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 8: Sucess rate - withdrawal/resumption due to hypertension or other clinical reason

Study or Subgroup	Discontinuation Events	Total	Continuation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Maland 1983	8	31	1	31	15.4%	5.99 [1.47 , 24.34]	
Myers 1982	4	38	6	39	17.4%	0.65 [0.17 , 2.45]	
Walma 1997	34	102	9	100	67.2%	4.24 [2.17 , 8.31]	
Total (95% CI)		**171**		**170**	**100.0%**	**3.23 [1.86 , 5.61]**	
Total events:	46		16				

Heterogeneity: Chi² = 7.00, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 4.17 (P < 0.0001)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours discontinuation — Favours continuation

Analysis 1.9. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 9: Quality of life

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Moonen 2015 (1)	-0.14	1.1558	180	-0.04	1.2099	176	100.0%	-0.10 [-0.35 , 0.15]	
Total (95% CI)			**180**			**176**	**100.0%**	**-0.10 [-0.35 , 0.15]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable

-1 -0.5 0 0.5 1
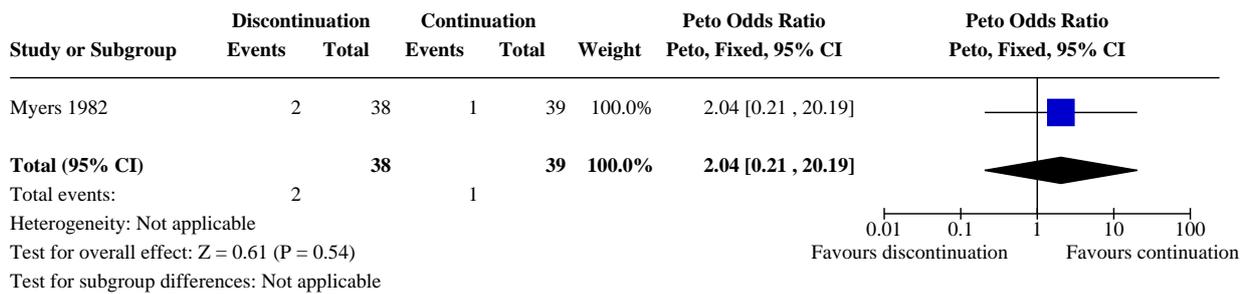Favours continuation — Favours discontinuation

Footnotes
(1) 16 weeks follow-up

Analysis 1.10. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 10: Systolic blood pressure subgrouped on duration
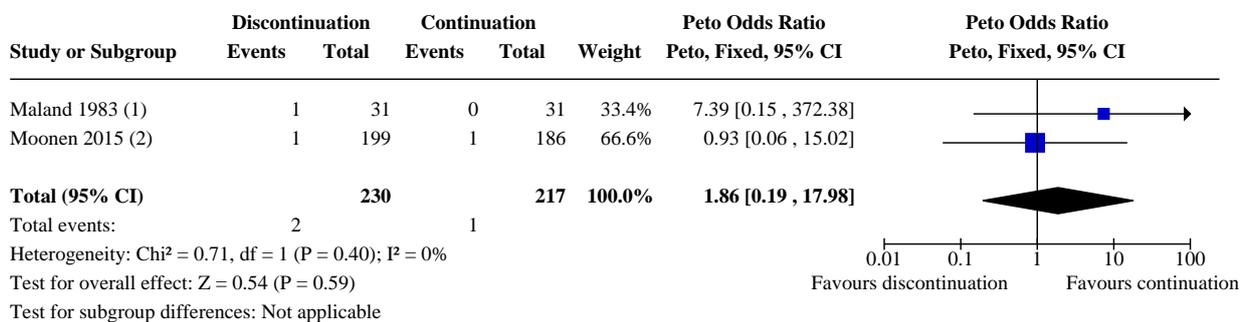
Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.10.1 Less than 12 months									
Burr 1977 (1)	136.3	12.7	41	131.8	12	48	22.0%	4.50 [-0.66 , 9.66]	
Moonen 2015 (2)	5.4	21.46625258	180	-2	19.8997487421324	176	31.7%	7.40 [3.10 , 11.70]	
Walma 1997 (3)	8.8	17.31	102	-4.7	11.0875	100	36.6%	13.50 [9.50 , 17.50]	
Subtotal (95% CI)			**323**			**324**	**90.4%**	**9.17 [6.62 , 11.71]**	
Heterogeneity: Chi² = 8.30, df = 2 (P = 0.02); I² = 76%									
Test for overall effect: Z = 7.05 (P < 0.00001)									
1.10.2 12 months or longer									
Maland 1983 (4)	143.2	23.45548976252679	31	122.8	19.79898987322333	31	5.0%	20.40 [9.59 , 31.21]	
Myers 1982 (5)	135	23.45548976252679	26	125.3	19.79898987322333	32	4.6%	9.70 [-1.63 , 21.03]	
Subtotal (95% CI)			**57**			**63**	**9.6%**	**15.30 [7.48 , 23.12]**	
Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%									
Test for overall effect: Z = 3.84 (P = 0.0001)									
Total (95% CI)			**380**			**387**	**100.0%**	**9.75 [7.33 , 12.18]**	
Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%									
Test for overall effect: Z = 7.89 (P < 0.00001)									
Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.3%									

-50 -25 0 25 50
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 16 weeks follow-up
(3) 6 months follow-up
(4) 12 months follow-up, SD imputed
(5) 12 months follow-up

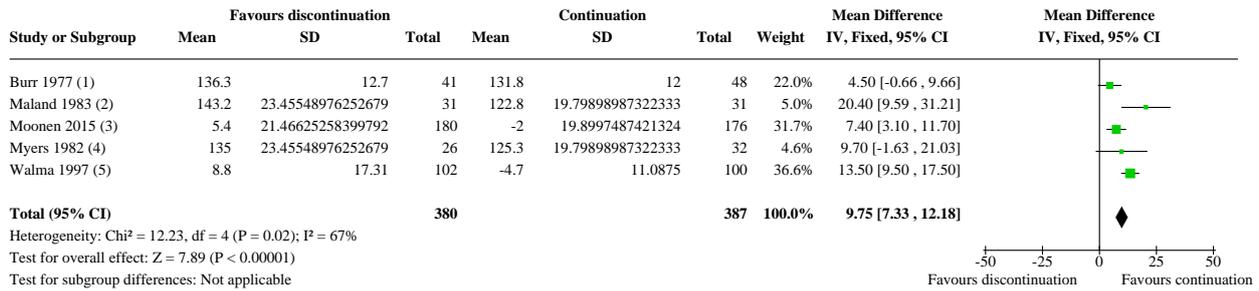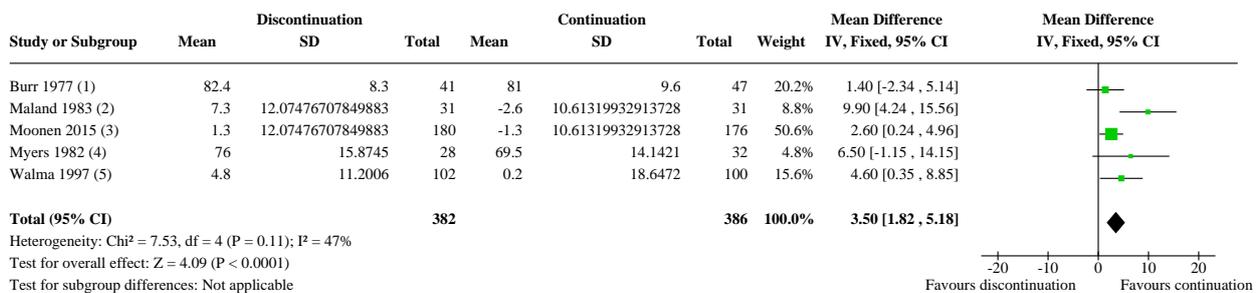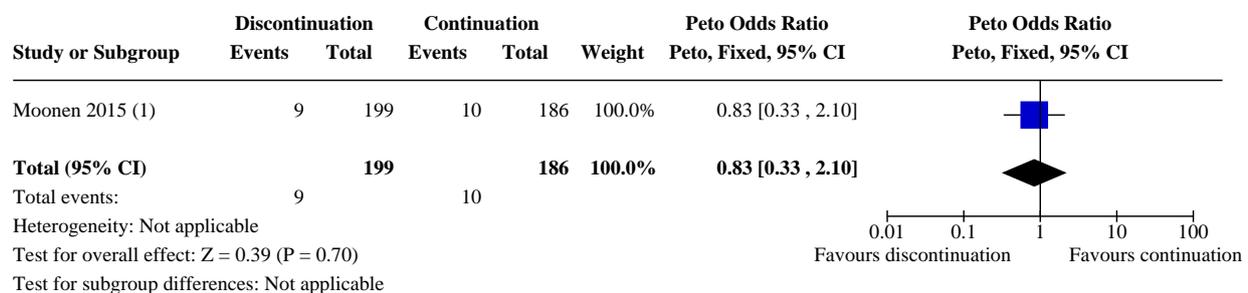## Analysis 1.11. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 11: Systolic blood pressure subgrouped on drug type

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.11.1 Diuretics									
Burr 1977 (1)	136.3	12.7	41	131.8	12	48	22.0%	4.50 [-0.66 , 9.66]	
Maland 1983 (2)	143.2	23.45548976252679	31	122.8	19.79898987322333	31	5.0%	20.40 [9.59 , 31.21]	
Myers 1982 (3)	135	23.45548976252679	26	125.3	19.79898987322333	32	4.6%	9.70 [-1.63 , 21.03]	
Walma 1997 (4)	8.8	17.31	102	-4.7	11.0875	100	36.6%	13.50 [9.50 , 17.50]	
Subtotal (95% CI)			**200**			**211**	**68.3%**	**10.85 [7.92 , 13.78]**	
Heterogeneity: Chi² = 10.54, df = 3 (P = 0.01); I² = 72%									
Test for overall effect: Z = 7.25 (P < 0.00001)									
1.11.2 Other									
Moonen 2015 (5)	5.4	21.46625258399792	180	-2	19.8997487421324	176	31.7%	7.40 [3.10 , 11.70]	
Subtotal (95% CI)			**180**			**176**	**31.7%**	**7.40 [3.10 , 11.70]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.37 (P = 0.0007)									
Total (95% CI)			**380**			**387**	**100.0%**	**9.75 [7.33 , 12.18]**	
Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%									
Test for overall effect: Z = 7.89 (P < 0.00001)									
Test for subgroup differences: Chi² = 1.69, df = 1 (P = 0.19), I² = 40.8%									

-50 -25 0 25 50
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 12 months follow-up, SD imputed
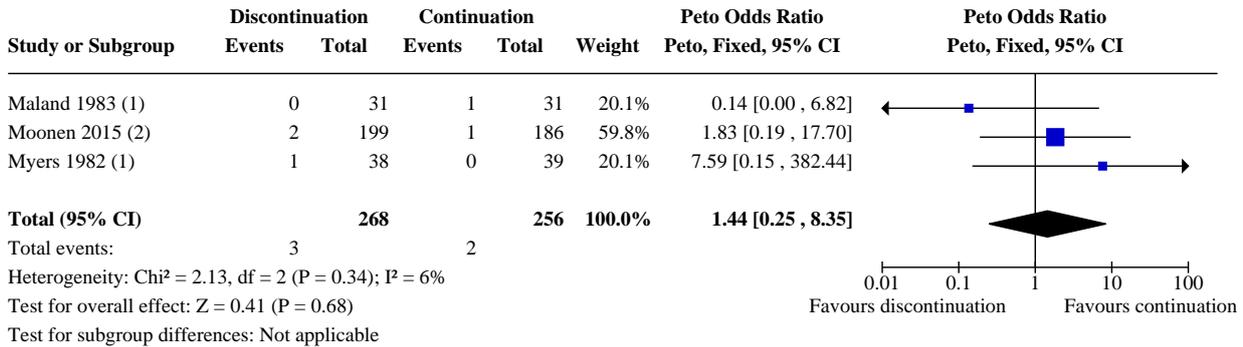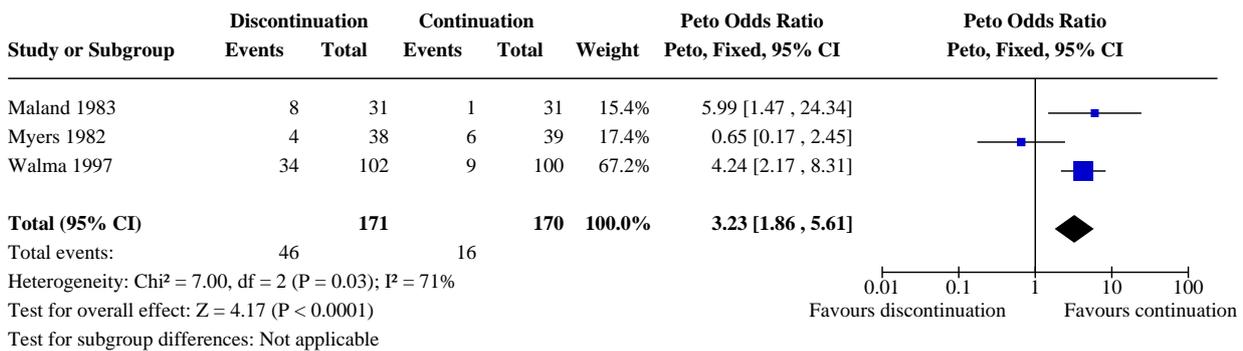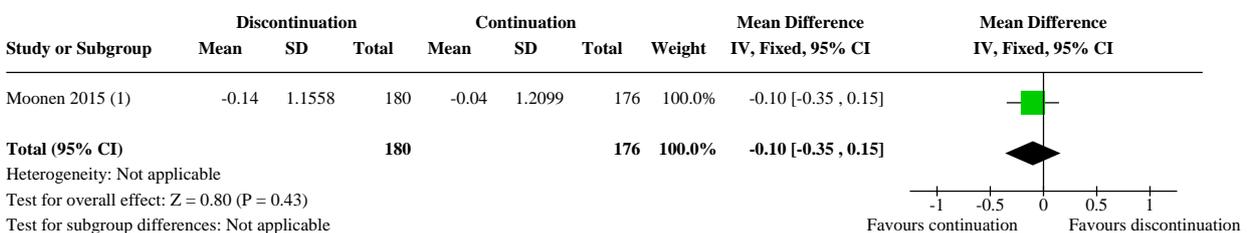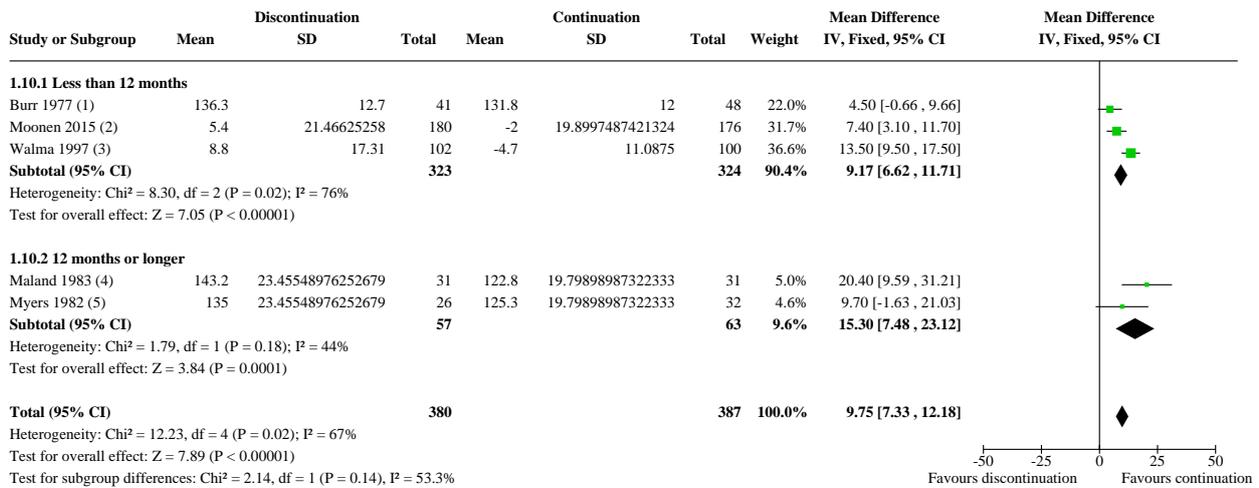(3) 12 months follow-up
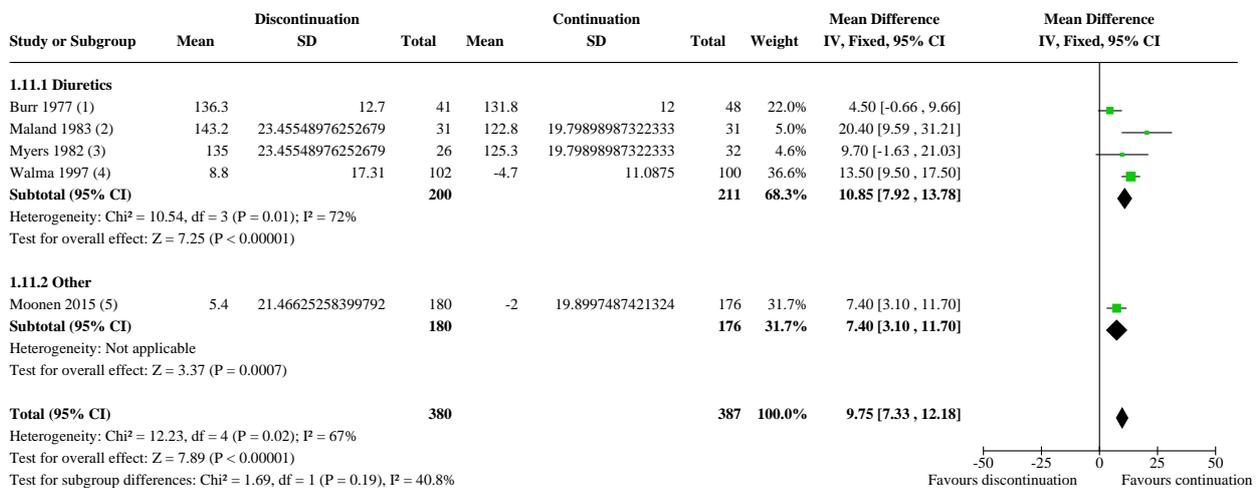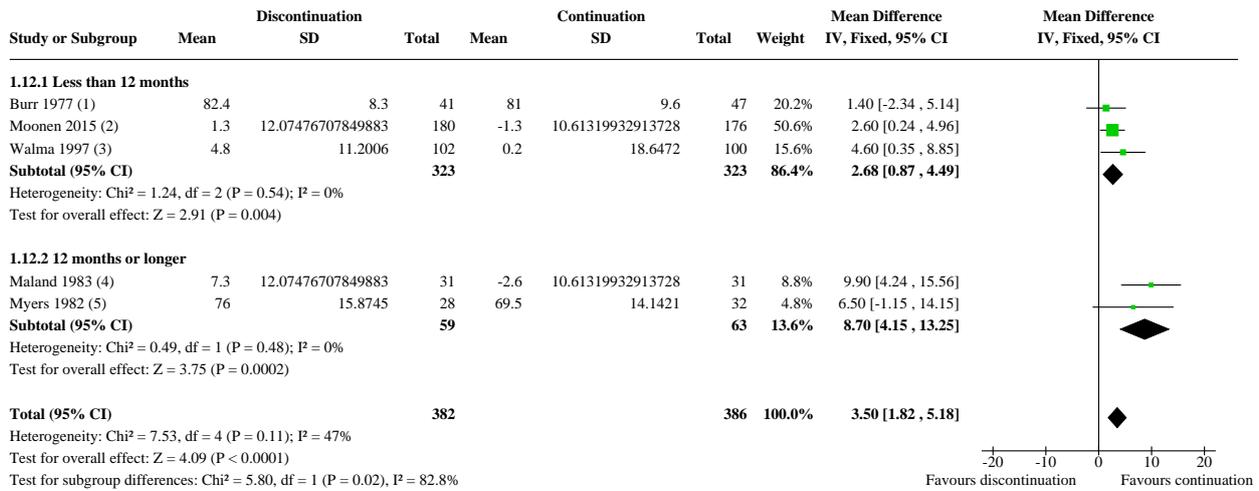(4) 6 months follow-up
(5) 16 weeks follow-up

Analysis 1.12. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 12: Diastolic blood pressure subgrouped on duration

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.12.1 Less than 12 months									
Burr 1977 (1)	82.4	8.3	41	81	9.6	47	20.2%	1.40 [-2.34 , 5.14]	
Moonen 2015 (2)	1.3	12.07476707849883	180	-1.3	10.61319932913728	176	50.6%	2.60 [0.24 , 4.96]	
Walma 1997 (3)	4.8	11.2006	102	0.2	18.6472	100	15.6%	4.60 [0.35 , 8.85]	
Subtotal (95% CI)			**323**			**323**	**86.4%**	**2.68 [0.87 , 4.49]**	
Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%									
Test for overall effect: Z = 2.91 (P = 0.004)									
1.12.2 12 months or longer									
Maland 1983 (4)	7.3	12.07476707849883	31	-2.6	10.61319932913728	31	8.8%	9.90 [4.24 , 15.56]	
Myers 1982 (5)	76	15.8745	28	69.5	14.1421	32	4.8%	6.50 [-1.15 , 14.15]	
Subtotal (95% CI)			**59**			**63**	**13.6%**	**8.70 [4.15 , 13.25]**	
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%									
Test for overall effect: Z = 3.75 (P = 0.0002)									
Total (95% CI)			**382**			**386**	**100.0%**	**3.50 [1.82 , 5.18]**	
Heterogeneity: Chi² = 7.53, df = 4 (P = 0.11); I² = 47%									
Test for overall effect: Z = 4.09 (P < 0.0001)									
Test for subgroup differences: Chi² = 5.80, df = 1 (P = 0.02), I² = 82.8%									

-20 -10 0 10 20
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 16 weeks follow-up
(3) 6 months follow-up
(4) 12 months follow-up, SD imputed
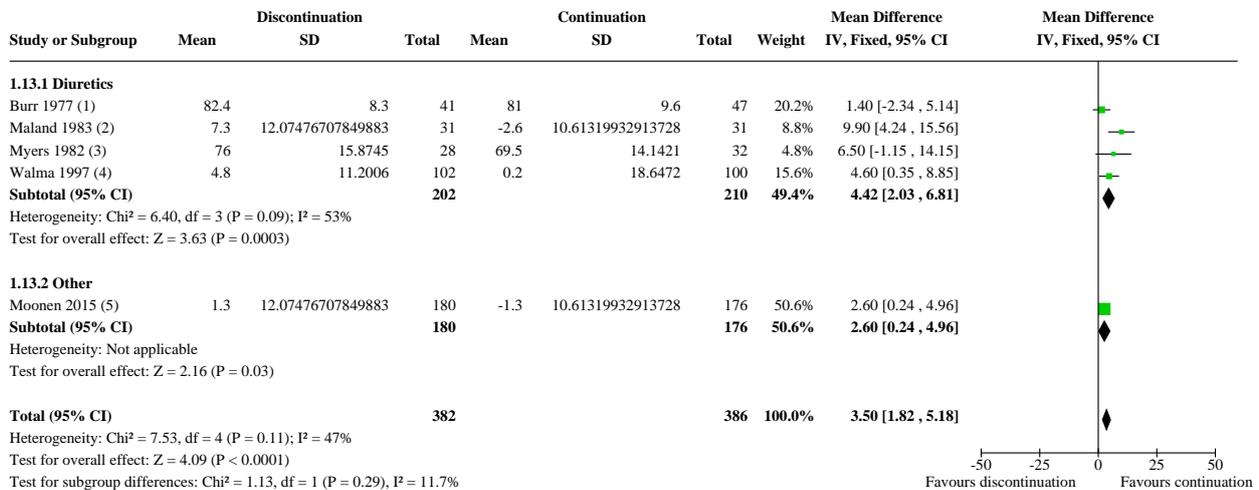(5) 12 months follow-up

Analysis 1.13. Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 13: Diastolic blood pressure subgrouped on drug type

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.13.1 Diuretics									
Burr 1977 (1)	82.4	8.3	41	81	9.6	47	20.2%	1.40 [-2.34 , 5.14]	
Maland 1983 (2)	7.3	12.07476707849883	31	-2.6	10.61319932913728	31	8.8%	9.90 [4.24 , 15.56]	
Myers 1982 (3)	76	15.8745	28	69.5	14.1421	32	4.8%	6.50 [-1.15 , 14.15]	
Walma 1997 (4)	4.8	11.2006	102	0.2	18.6472	100	15.6%	4.60 [0.35 , 8.85]	
Subtotal (95% CI)			**202**			**210**	**49.4%**	**4.42 [2.03 , 6.81]**	
Heterogeneity: Chi² = 6.40, df = 3 (P = 0.09); I² = 53%									
Test for overall effect: Z = 3.63 (P = 0.0003)									
1.13.2 Other									
Moonen 2015 (5)	1.3	12.07476707849883	180	-1.3	10.61319932913728	176	50.6%	2.60 [0.24 , 4.96]	
Subtotal (95% CI)			**180**			**176**	**50.6%**	**2.60 [0.24 , 4.96]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.16 (P = 0.03)									
Total (95% CI)			**382**			**386**	**100.0%**	**3.50 [1.82 , 5.18]**	
Heterogeneity: Chi² = 7.53, df = 4 (P = 0.11); I² = 47%									
Test for overall effect: Z = 4.09 (P < 0.0001)									
Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.7%									

-50 -25 0 25 50
Favours discontinuation   Favours continuation

Footnotes
(1) 5-12 weeks follow-up
(2) 12 months follow-up, SD imputed
(3) 12 months follow-up
(4) 6 months follow-up
(5) 16 weeks follow-up

ADDITIONAL TABLES

Table 1. Summary of studies

Study, country	Setting	Study duration	Antihypertensive medication class withdrawn	Discontinuation plan
Burr 1977, Wales	Long-stay geriatric wards	12 months	Diuretic	Not specified
Langford 1984, USA	Primary care	56 weeks	Any antihypertensive medication	Participants were withdrawn from therapy using a standardised step-down withdrawal programme taking from 2 to 8 weeks, depending on the number and dosage of drugs at entry. The diuretic was the last agent withdrawn. Drug withdrawal took place in a stepped fashion with the highest step drug being removed first. Target time for withdrawal was 6 weeks.
Maland 1983, USA	Community	12 months	Diuretic	Not specified
Moonen 2015, Netherlands	128 general practices	16 weeks	β-Blocker, diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or calcium channel blocker.	The discontinuation of antihypertensive treatment was performed by the participant's physician according to an algorithm composed by the investigators. All physicians were instructed to withdraw antihypertensive treatment until a maximum increase of 20 mmHg in SBP was reached. The physician monitored BP every week until no further changes in antihypertensive treatment were made
Myers 1982, Canada	Geriatric institution	12 months	Diuretic	Not specified
Walma 1997, Netherlands	8 general practices	6 months	Diuretic	Participants with frusemide dosages of 40 or 80 mg/day went through a dose-halving regimen of one and two weeks, respectively, to prevent severe rebound effects. Dose halving was started immediately after randomisation and was performed double-blind.

BP: Blood pressure
SBP: Systolic blood pressure

APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 19, 2019>
Search Date: 22 April 2019
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1 exp aged/
2 middle aged/

3 (advanced years or ageing or aging or elder$ or elderly or frail or geriatric? or gerontolog$ or later life or middle aged or midlife or nursing care or nursing home? or old age or oldest old or pensioner? or post-menopausal or postmenopausal or senior or seniors).mp.

4 (old$ adj3 (adult? or female? or male? or men or people or person or women)).tw,kf.

5 ((over or older) adj2 ("49" or "50" or "51" or "52" or "53" or "54" or "55" or "56" or "57" or "58" or "59" or "60" or "61" or "62" or "63" or "64" or "65" or "66" or "67" or "68" or "69" or "70" or "71" or "72" or "73" or "74" or "75" or "76" or "77" or "78" or "79" or "80" or "81" or "82" or "83" or "84" or "85" or "86" or "87" or "88" or "89" or "90" or "91" or "92" or "93" or "94" or "95" or "96" or "97" or "98" or "99" or "100") adj years).tw.

6 (aged or aging or ageing or elder$ or geriatric$ or gerontolog$).jw,nw.

7 or/1-6

8 hypertension/

9 essential hypertension/

10 (antihypertens$ or hypertens$).tw,kf.

11 ((elevat$ or high$ or raised) adj2 (bp or blood pressure)).tw,kf.

12 or/8-11

13 exp antihypertensive agents/

14 exp thiazides/

15 exp sodium chloride symporter inhibitors/

16 exp sodium potassium chloride symporter inhibitors/

17 ((ceiling or loop) adj diuretic?).tw,kf.

18 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw,kf.

19 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw,kf.

20 or/14-19

21 exp angiotensin-converting enzyme inhibitors/

22 angiotensin converting enzyme inhibit$.tw,kf.

23 (ace adj2 inhibit$).tw,kf.

24 acei.tw,kf.

25 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw,kf.

26 or/21-25

27 exp Angiotensin Receptor Antagonists/

28 (angiotensin adj3 receptor antagon$).tw,kf.

29 (angiotensin adj3 receptor block$).tw,kf.

30 (arb or arbs).tw,kf.

31 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw,kf.

32 or/27-31

33 exp calcium channel blockers/

34 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw,kf.

35 (calcium adj2 (antagonist? or block$ or inhibit$)).tw,kf.

36 or/33-35

37 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.

38 (reserpine or serpentina or rauwolfia or serpasil).mp.

39 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.

40 exp hydralazine/

41 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw,kf.

42 or/37-41

43 exp adrenergic beta-antagonists/

44 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw,kf.

45 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw,kf.

46 or/43-45

47 exp adrenergic alpha antagonists/

48 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw,kf.

49 (adrenergic adj2 (alpha or antagonist?)).tw,kf.

50 ((adrenergic or alpha or receptor?) adj2 block$).tw,kf.

51 or/47-50

52 13 or 20 or 26 or 32 or 36 or 42 or 46 or 51

53 withdraw$.tw,kf.

54 (ceased or ceasing or cessation$).tw,kf.

55 (deprescrib$ or discontinu$).tw,kf.

56 ((reduced or reduces or reducing or reduction?) adj4 (antihypertens$ or anti-hypertens$ or dosage? or dose or doses or drug$ or medicat$ or prescri$)).tw,kf.

57 stop$.tw,kf.

58 taper$.tw,kf.

59 or/53-58

60 randomized controlled trial.pt.

61 controlled clinical trial.pt.

62 randomized.ab.

63 placebo.ab.

64 clinical trials as topic/

65 randomly.ab.

66 trial.ti.

67 or/60-66

68 animals/ not (humans/ and animals/)

69 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/

70 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti.

71 67 not (68 or 69 or 70) (

72 7 and 12 and 52 and 59 and 71

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies

Search Date: 22 May 2019

#1 (ageing OR aging OR elder* OR frail OR geriatric* OR middle aged OR nursing care OR nursing home* OR old age OR older OR pensioner* OR postmenopausal OR post-menopausal OR senior OR seniors) AND INREGISTER

#2 ((49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100) NEXT years) AND INREGISTER

#3 (#1 OR #2) AND INSEGMENT

#4 (antihypertens* OR hypertens* OR elevated blood pressure OR high* blood pressure OR raised blood pressure) AND INREGISTER

#5 (ceased OR ceasing OR cessation OR deprescrib* OR discontinu* OR stop* OR taper* OR withdraw*) AND INREGISTER

#6 RCT: DE AND INREGISTER

#7 Review:ODE AND INREGISTER

#8 (#6 OR #7) AND INREGISTER

#9 (#3 AND #4 AND #5 AND #8) AND INREGISTER

Cochrane
Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies
Search Date: 22 April 2019

#1 (ageing OR aging OR elder* OR frail OR geriatric* OR middle aged OR nursing care OR nursing home* OR old age OR older OR pensioner* OR postmenopausal OR post-menopausal OR senior OR seniors) AND CENTRAL:TARGET
#2 ((49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100) NEXT years) AND CENTRAL:TARGET
#3 (#1 OR #2) AND CENTRAL:TARGET
#4 (antihypertens* OR hypertens* OR elevated blood pressure OR high* blood pressure OR raised blood pressure) AND CENTRAL:TARGET
#5 (ceased OR ceasing OR cessation OR deprescrib* OR discontinu* OR stop* OR taper* OR withdraw*) AND CENTRAL:TARGET
#6 (#3 AND #4 AND #5) AND CENTRAL:TARGET
#7 #6 AND INREGISTER:TARGET
#8 #6 NOT #7 AND CENTRAL:TARGET

Database: Embase <1974 to 2019 April 19>
Search Date: 22 April 2019
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1 exp aged/
2 middle aged/
3 (advanced years or ageing or aging or elder$ or elderly or frail or geriatric? or gerontolog$ or later life or middle aged or midlife or nursing care or nursing home? or old age or oldest old or pensioner? or post-menopausal or postmenopausal or senior or seniors).mp.
4 (old$ adj3 (adult? or female? or male? or men or people or person or women)).tw.
5 ((over or older) adj2 ("49" or "50" or "51" or "52" or "53" or "54" or "55" or "56" or "57" or "58" or "59" or "60" or "61" or "62" or "63" or "64" or "65" or "66" or "67" or "68" or "69" or "70" or "71" or "72" or "73" or "74" or "75" or "76" or "77" or "78" or "79" or "80" or "81" or "82" or "83" or "84" or "85" or "86" or "87" or "88" or "89" or "90" or "91" or "92" or "93" or "94" or "95" or "96" or "97" or "98" or "99" or "100") adj years).tw.
6 (aged or aging or ageing or elder$ or geriatric$ or gerontolog$).jw,nw.
7 or/1-6
8 exp hypertension/
9 (antihypertens$ or hypertens$).tw.
10 ((elevat$ or high$ or raised) adj2 (bp or blood pressure)).tw.
11 or/8-10
12 exp antihypertensive agent/
13 exp thiazide diuretic agent/
14 exp loop diuretic agent/
15 ((ceiling or loop) adj diuretic?).tw.
16 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw.
17 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw.
18 or/13-17
19 exp dipeptidyl carboxypeptidase inhibitor/
20 angiotensin converting enzyme inhibit$.tw.
21 (ace adj2 inhibit$).tw.
22 acei.tw.
23 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw.
24 or/19-23
25 exp angiotensin receptor antagonist/
26 (angiotensin adj3 receptor antagon$).tw.
27 (angiotensin adj3 receptor block$).tw.
28 (arb or arbs).tw.
29 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw.
30 or/25-29
31 exp calcium channel blocking agent/

32 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw.

33 (calcium adj2 (antagonist? or block$ or inhibit$)).tw.

34 or/31-33

35 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.

36 (reserpine or serpentina or rauwolfia or serpasil).mp.

37 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.

38 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw.

39 or/35-38

40 exp beta adrenergic receptor blocking agent/

41 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw.

42 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw.

43 or/40-42

44 exp alpha adrenergic receptor blocking agent/

45 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw.

46 (adrenergic adj2 (alpha or antagonist?)).tw.

47 ((adrenergic or alpha or receptor?) adj2 block$).tw.

48 or/44-47

49 12 or 18 or 24 or 30 or 34 or 39 or 43 or 48

50 withdraw$.tw.

51 (ceased or ceasing or cessation$).tw.

52 (deprescrib$ or discontinu$).tw.

53 ((reduced or reduces or reducing or reduction?) adj4 (antihypertens$ or anti-hypertens$ or dosage? or dose or doses or drug$ or medicat$ or prescri$)).tw.

54 stop$.tw.

55 taper$.tw.

56 or/50-55

57 randomized controlled trial/

58 crossover procedure/

59 double-blind procedure/

60 (randomi?ed or randomly).tw.

61 (crossover$ or cross-over$).tw.

62 placebo.ab.

63 (doubl$ adj blind$).tw.

64 assign$.ab.

65 allocat$.ab.

66 or/57-65

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

68 exp pregnancy/ or maternal hypertension.mp. or exp pregnancy complication/ or intraocular hypertension/

69 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti.

70 66 not (67 or 68 or 69)

71 7 and 11 and 49 and 56 and 70

Database: ClinicalTrials.gov
Search Date: 22 April 2019

Condition or disease: Hypertension
Other terms: randomized
Study Type: Interventional Studies (Clinical Trials)
Intervention/treatment: ceased OR ceasing OR cessation OR deprescrib* OR discontinu* OR stop* OR taper* OR withdrawal

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Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 22 April 2019

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hypertens* AND elder* AND randomized AND ceased
hypertens* AND older AND randomized AND ceased
hypertens* AND elder* AND randomized AND ceasing
hypertens* AND older AND randomized AND ceasing
hypertens* AND elder* AND randomized AND cessation
hypertens* AND older AND randomized AND cessation
hypertens* AND elder* AND randomized AND deprescrib*
hypertens* AND older AND randomized AND deprescrib*
hypertens* AND elder* AND randomized AND discontinu*
hypertens* AND older AND randomized AND discontinu*
hypertens* AND elder* AND randomized AND stop*
hypertens* AND older AND randomized AND stop*
hypertens* AND elder* AND randomized AND taper*
hypertens* AND older AND randomized AND taper*
hypertens* AND aged AND randomized AND withdraw*
hypertens* AND elder* AND randomized AND withdraw*
hypertens* AND older AND randomized AND withdraw*
hypertens* AND elder* and randomized

Database: Epistemonikos
Search Date: 22 April 2019

(title:(hypertens* OR elevated blood pressure OR high blood pressure) OR abstract:(hypertens* OR elevated blood pressure OR high blood pressure)) AND (title:(advanced years OR ageing OR aging OR elder* OR elderly OR frail OR geriatric* OR gerontology* OR later life OR middle aged OR nursing care OR nursing home* OR old age OR oldest old OR pensioner* OR post-menopausal OR postmenopausal OR senior OR seniors) OR abstract:(advanced years OR ageing OR aging OR elder* OR elderly OR frail OR geriatric* OR gerontology* OR later life OR middle aged OR nursing care OR nursing home* OR old age OR oldest old OR pensioner* OR post-menopausal OR postmenopausal OR senior OR seniors))
AND
Publication type: Systematic Review

HISTORY

Protocol first published: Issue 2, 2017
Review first published: Issue 6, 2020

Date	Event	Description
27 February 2017	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

ER: Conceived and designed the protocol, screened abstracts and full texts, extracted data and conducted 'Risk of bias' assessment, interpretation of data analysis and grading, narrative synthesis of results, drafted the manuscript, reviewed and revised the manuscript.

VJ: Conceived and designed the protocol, screened abstracts and full texts, conducted analysis, drafted the manuscript, reviewed and revised the manuscript.

WT: Screened abstracts and full texts, extracted data and conducted 'Risk of bias' assessment, contributed to the text, reviewed and revised the manuscript.

MS: Screened abstracts and full texts, extracted data and conducted 'Risk of bias' assessment, contributed to the text, reviewed and revised the manuscript.

AT: Screened abstracts and full texts, extracted data and conducted 'Risk of bias' assessment, contributed to the text, reviewed and revised the manuscript.

TG: Conceived and designed the protocol, screened abstracts and full texts, contributed to the text, reviewed and revised the manuscript.

IH: Conceived and designed the protocol, screened abstracts, contributed to the text, reviewed and revised the manuscript.

SH: Conceived and designed the protocol, contributed to the text, reviewed the manuscript.

DG: Conceived and designed the protocol, screened abstracts and full texts, extracted data and conducted 'Risk of bias' assessment, drafted the manuscript, reviewed and revised the manuscript.

DECLARATIONS OF INTEREST

SOURCES OF SUPPORT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We determined additional criteria to clarify articles for inclusion related to the age cut-off. Specifically: to be eligible, all participants had to be aged 50 years or older, results for participants aged 50 years and older were presented in a separate subgroup analysis or the majority of participants were 50 years or older (as determined by looking at mean/median age and standard deviation (SD)/interquartile range (IQR)) (to be included, the mean age minus the SD must be >/= 50 years, or, if IQR, three-quarters of participants must be >/= 50 years old, or the article reported the number of people >/= 50 years old). We also clarified 'primary prevention of cardiovascular disease' by adding criteria relevant to this: if the reported indication in the study was hypertension or primary prevention of cardiovascular disease and less than 20% of the population had reported cardiovascular disease at baseline.

Different authors participated in the screening, data extraction and 'Risk of bias assessment' than had been planned in the protocol.

As a result of conflicting protocol methods in the measures of treatment effect and data synthesis sections, we have standardised these to both state Peto odds ratios and used this as the analysis method. Peto odds ratios were appropriate due to the rare nature of the primary outcomes. The use of Peto odds ratios necessitated the use of the fixed effect model. Previously the protocol had noted that we would use random-effects models due to anticipated heterogeneity, or where heterogeneity was found.