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Withdrawal of antihypertensive drugs in older people

Table of contents

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Abstract

Background

Hypertension is an important risk factor for subsequent cardiovascular events, including ischaemic and haemorrhagic stroke, myocardial infarction, and heart failure, as well as 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 evaluate the effects of withdrawal of antihypertensive medications used for hypertension or primary prevention of cardiovascular disease (CVD) in older adults.

This is an update of a review published in 2020.

Search methods

For this update, we searched the Cochrane Hypertension Specialised Register, CENTRAL (2022, Issue 9), Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov up to October 2022. 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 all the antihypertensive medication, and those focusing on a dose reduction of the antihypertensive medication.

Data collection and analysis

We compared the intervention of discontinuing or reducing the dose of 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, and development of adverse drug reactions or adverse drug withdrawal reactions. Secondary outcomes included: hospitalisation, stroke, blood pressure (systolic and diastolic), falls, quality of life, and success of withdrawing from antihypertensives. Two authors independently, and in duplicate, conducted all stages of study selection, data extraction and quality assessment.

Main results

No new studies were identified in this update. Six RCTs from the original review 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, discontinuing antihypertensives (compared to continuing) may result in little to no difference in all-cause mortality (OR 2.08, 95% CI 0.79 to 5.46; P = 0.14, I^2 = 0%; 4 studies, 630 participants; low certainty of evidence), and the evidence is very uncertain about the effect on myocardial infarction (OR 1.86, 95% CI 0.19 to 17.98; P = 0.59, I^2 = 0%; 2 studies, 447 participants; very low certainty of evidence). For the development of adverse drug reactions and withdrawal reactions, meta-analysis was not possible; the evidence was very uncertain about the effect of antihypertensive discontinuation on the risk of adverse drug reactions (very low certainty of evidence) and eligible studies did not assess adverse drug *withdrawal* reactions specifically. One study reported on hospitalisations; discontinuing antihypertensives may result in little to no difference in hospitalisation (OR 0.83, 95% CI 0.33 to 2.10; P = 0.70; 1 study, 385 participants; low certainty of evidence). Meta-analysis showed that discontinuing antihypertensives may result in little to no difference in stroke (OR 1.44, 95% CI 0.25 to 8.35; P = 0.68, I^2 = 6%; 3 studies, 524 participants; low certainty of evidence). Blood pressure may be higher in the discontinuation group than the continuation group (systolic blood pressure: MD 9.75 mmHg, 95% CI 7.33 to 12.18; P < 0.001, I^2 = 67%; 5 studies, 767 participants; low certainty of evidence; and diastolic blood pressure: MD 3.5 mmHg, 95% CI 1.82 to 5.18; P < 0.001, I^2 = 47%; 5 studies, 768 participants; low certainty of evidence). No studies were identified which reported falls. 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

The main conclusions from the 2020 review still apply. Discontinuing antihypertensives may result in little to no difference in mortality, hospitalisation and stroke. The evidence is very uncertain about the effect of discontinuing antihypertensives on myocardial infarction and adverse drug reactions and adverse drug withdrawal reactions. Discontinuing antihypertensives may result in an increase in blood pressure. There was no information about the effect on falls. 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 adverse drug events, falls and quality of life.

Plain language summary

Stopping blood pressure medications in older people

Key Messages

Due to a lack of robust evidence, the benefits and risks of stopping blood pressure medications in older people who are taking the medication for high blood pressure or primary prevention of heart disease is unclear.

Future research into the effects of stopping blood pressure medications should focus on older adults who are at the highest risk of side effects. This includes people taking multiple medications and people living with frailty.

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

What is hypertension?

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.

Why would blood pressure medications be stopped?

Overtime, both the benefits and harms of medications can change. Blood pressure medications 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 blood pressure medications outweigh the harms in older people.

What did we want to find out?

This review aimed to find out the effects of stopping these medications.

What did we do?

We searched for studies that compared stopping or reducing the dose of blood pressure medications with continuing blood pressure medications.

We included studies with 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).

What did we find?

We found no new studies in this update. Our original review found six studies, including 1,073 older adults in total. Studies lasted from 4 to 56 weeks long. People in the studies had an average age of 58 to 82 years. In three of the studies, the dose of the blood pressure medication was slowly lowered before stopping.

We found that stopping blood pressure medications may make little to no difference on the risk of death.

Stopping blood pressure medications may have little to no effect on having a heart attack, but we are very uncertain about the results.

Stopping blood pressure medications may have little to no effect on the risk of adverse drug reactions, but this was not reported well, and so we are very uncertain about the results.

Stopping blood pressure medications may make little to no difference to the risk of hospitalisation or stroke.

Stopping blood pressure medications may increase blood pressure.

We found no studies which reported whether stopping blood pressure medications affects falls.

What are the limitations of the evidence?

We have little to no confidence in the evidence because:

- it is possible that the people in the studies were aware of which treatment they were getting and some of the studies did not report all the information that we were interested in,

- the evidence is based on a small number of death, heart attacks, hospitalisation and stroke,

- most of the studies were conducted over 30 years ago, the standards of care have changed since then, and

- the results from the studies varied widely.

How up to date is this evidence?

This review updates our previous review published in 2020 (search conducted in April 2019). The evidence is up-to-date to October 2022.

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	Low risk 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 risk population					

	26 per 1,000	52 per 1,000 (20 to 126)				
Myocardial infarction (fatal and nonfatal) follow-up: range 16 weeks to 12 months	Low risk 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 risk population					
	3 per 1,000	5 per 1,000 (1 to 46)				
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 [7] [8]	
Hospitalisation follow-up: 16 weeks	Low risk population		OR 0.83 (0.33 to 2.10)	385 (1 RCT)	⊕⊕⊖⊖ LOW [9]	
	54 per 1,000	45 per 1,000 (18 to 107)				
Stroke (fatal + nonfatal + TIA) follow-up: range 16 weeks to 12 months	Low risk population		OR 1.44 (0.25 to 8.35)	524 (3 RCTs)	⊕⊕⊖⊖ LOW [3] [10]	
	8 per 1,000	11 per 1,000 (2 to 62)				
	Moderate risk population					
	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 [11]	MD 9.75 mmHg higher (7.33 higher to 12.18 higher)	-	767 (5 RCTs)	⊕⊕⊖⊖ LOW [12] [13] [14]	
Diastolic blood pressure: range 12 weeks to 12 months	The mean diastolic blood pressure ranged from 70-95 mmHg [11]	MD 3.5 mmHg higher (1.82 higher to 5.18 higher)	-	768 (5 RCTs)	⊕⊕⊖⊖ LOW [12] [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 myocardial infarction 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 risk of bias due to very serious concern about lack of blinding, attrition bias and poor detection and reporting of outcome.

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

[9] 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.

[10] 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)..

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

[12] 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.

[13] 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.

[14] 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.

[15] 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.

TIA: Transient ischaemic attack

Background

This review is an update of the Cochrane Review 'Withdrawal of antihypertensive drugs in older people' published in 2020 (original search date April 2019) (Reeve 2020).

Description of the condition

The prevalence of hypertension or high blood pressure (BP) increases with age, affecting 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 and heart failure, as well as 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 BP when changing from a sitting or lying position to standing), falls and cognitive impairment (Parekh 2017; Chatzis 2023). Antihypertensive medications can increase the risk of adverse drug reactions, 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) (Albasri 2021; Sheppard 2023). BP 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 medications simultaneously in an individual patient, and has been widely documented as a risk factor for adverse drug reactions, drug-disease and drug-drug interactions as well as increased morbidity and mortality, and costs (Reeve 2014; Steinman 2006; Wastesson 2018; Lee 2022). 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 (Reeve 2014; Scott 2015; Gnjidic 2021).

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 (NICE 2022). 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 as well as the individual's values and preferences, 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; Weir 2022).

Withdrawal of antihypertensive medications can either be complete (immediate) discontinuation of all prescribed 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 all 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 adverse drug reactions (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

This is an update of a Cochrane review first published in 2020.

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; Albasri 2021; Sheppard 2023). 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), included studies with participants with a history of CVD (Crisafulli 2021) or primarily focused on the effect of medication withdrawal interventions on cognition in older people (Jongstra 2016).

Given the lack of certainty in the evidence in our original review with respect to benefits and harms of withdrawing antihypertensives in older adults, and the need for high quality data, an update of the original review was conducted to include new relevant studies.

Thus, this updated review provides up-to-date evidence and investigates a number of clinically relevant outcomes of antihypertensive withdrawal in older people.

Objectives

To evaluate the effects of withdrawal of antihypertensive medications used for hypertension or primary prevention of CVD in older adults.

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;
- Angiotensin-converting enzyme (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.

While they are not used as first or second line treatment for hypertension or primary prevention of CVD, we also included alpha-blockers and clonidine:

- alpha-blockers act as antagonists on α-adrenergic receptors. Arteriolar and venous vasodilation results in decreased peripheral resistance and BP;
- clonidine is a centrally acting agonist at $alpha_2$ adrenoreceptors and imidazoline receptors, it reduces BP by reducing sympathetic tone.

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

- Hospitalisation (all-cause, cardiovascular hospitalisation, heart failure hospitalisation).
- Stroke (fatal and non-fatal, ischaemic and haemorrhagic, transient ischaemic attack).
- BP, including systolic and diastolic BP, before and after withdrawal of antihypertensive drugs and mean arterial pressure.
- Falls
- 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)).
- 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.

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:

- Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (to 24 November 2022);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 9) via the Cochrane Register of Studies;
- MEDLINE(R) ALL Ovid (1946 to 27 October 2022);
- Embase Ovid (1974 to 27 October 2022);
- EBSCO (all databases on platform, searched 27 October 2022);
- Clarivate Web of Science (searched 27 October 2022);
- Google Scholar via Harzing's Publish or Perish (Publish or Perish 2022, searched 27 October 2022);

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov, to 27 October 2022);
- World Health Organization International Clinical Trials Registry Platform (https://apps.who.int/trialsearch), to 28 October 2022).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with adaptations of the 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 6, (Higgins 2017)). 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

For this update, two review authors (out of DG, AL, WT, MS, and ER) 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 2017; 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 2017; 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 2017). 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 2017). We resolved disagreements through consultation with a third review author.

Data synthesis

We synthesised data for each study outcome separately using Revman Web (RevMan Web 2024), 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 MDs 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 2017). 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

Two independent assessors (DG and ER) 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 table 1. We preselected the following outcomes for inclusion in the Summary of findings table 1: mortality, myocardial infarction, adverse drug reactions, hospitalisation, stroke, BP (systolic and diastolic), and falls.

Results

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 830 new articles were identified from electronic databases in this update. No potentially releavnt studies were found from other sources. After de-duplication there were 813 studies which underwent title and abstract screening and, a total of 41 studies were obtained in full text and assessed for eligibility (Figure 1). We excluded all 41 studies (Characteristics of excluded studies). Twenty-eight studies were excluded due to wrong intervention,

four due to wrong population, eight due to wrong study design and one as one or more groups had confounding treatment. No additional eligible studies were found through hand searching of reference lists. Therefore, we did not identify any new studies to include in this update.

Included studies

As per the previous version of this review, 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 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 on 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: hospitalisation, one study (Moonen 2015); stroke, three studies, (Maland 1983; Moonen 2015; Myers 1982); systolic blood pressure (SBP) and diastolic blood pressure (DBP), five studies (Burr 1977; Maland 1983; Moonen 2015; Myers 1982; Walma 1997); QoL, one study (Moonen 2015); and success of withdrawal as measured by the ability to remain off the medication, four studies (Langford 1984; Maland 1983; Myers 1982; Walma 1997). 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

In this update, we excluded 41 studies (reasons for exclusion are shown in Characteristics of excluded studies) with the 33 studies previously excluded in the first version of this review). Four articles identified in the updated search were linked to studies identified and excluded in the initial search, resulting in a total of 70 studies excluded at the full-text level across both versions of this review. Reasons for exclusion in this update 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); or, one or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).

We contacted authors of one potentially eligible trial that was published as an abstract only, to determine eligibility. The trial was subsequently excluded as authors provided information that confirmed that the study population was

not eligible (greater than 20% of the cohort had any history of CVD).

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.

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 table 1.

Primary outcomes

Mortality

Four studies (Burr 1977; Maland 1983; Moonen 2015; Myers 1982) reported all-cause mortality; 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 630 participants, were included in a meta-analysis. Pooled data showed that discontinuation of antihypertensives, compared to continuation, may result in little to no difference in mortality (OR 2.08, 95% Confidence Interval (CI) 0.79 to 5.46; P = 0.14, I^2 = 0%; 4 studies, 630 participants; low certainty of evidence; Analysis 1.1). 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.

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. The evidence is very uncertain about the effect of distontinuing antihypertensives on cardiovascular mortality (OR 2.04, 95% CI 0.21 to 20.19; P = 0.54; 1 study, 77 participants; very low certainty of evidence; Analysis 1.2). One in each group died from heart failure and the second participant in the withdrawal group had a stroke (normal BP). The evidence was very low certainty.

Myocardial infarction

Two studies reported the outcome of myocardial infarctions and both were included in the meta-analysis; Maland 1983 had a 12-month follow-up and Moonen 2015 had a 16-week follow-up. The evidence is very uncertain about the effect of discontinuing antihypertensives on myocardial infarction (OR 1.86, 95% CI 0.19 to 17.98; P = 0.59, I^2 = 0%; 2 studies, 447 participants; very low certainty of evidence; 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. The evidence is very uncertain about the effect of antihypertensive discontinuation on the risk of adverse drug reactions and included studies did not report adverse drug *withdrawal* reactions specifically.

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 a small amount 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 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

Hospitalisation

Hospitalisation was reported as an outcome in a single study involving participants with mild cognitive defects (Moonen 2015). Evidence suggests that antihypertensive discontinuation results in little to no difference in hospitalisations (OR 0.83, 95% CI 0.33 to 2.10; P = 0.70; 1 study, 385 participants; low certainty of evidence; Analysis 1.4). 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. Pooled data showed that discontinuation may result in little to no difference in stroke (OR 1.44, 95% CI 0.25 to 8.35, P = 0.68, I^2 = 6%; 3 studies, 524 participants; low certainty of evidence; Analysis 1.5). The certainty of the evidence was determined to be low due to serious concerns about indirectness and imprecision.

Blood pressure (BP)

Five studies (n = 767) were included in a meta-analysis of SBP (Burr 1977; Maland 1983; Moonen 2015; Myers 1982; Walma 1997). Pooled data showed that discontinuation of antihypertensives may increase SBP compared to continuation (MD 9.75 mmHg, 95% CI 7.33 to 12.18, P < 0.001, I^2 = 67%; 5 studies, 767 participants; low certainty of evidence; Analysis 1.6). The certainty of the evidence was low.

Substantial heterogeneity (I^2 = 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 differences (P = 0.14) between the mean differences in the two

subgroups (duration of follow-up < 12 months: MD 9.17 mmHg, 95% CI 6.62 to 11.71; P < 0.001, I^2 = 76%; 3 studies, 647 participants; duration of follow-up ≥ 12 months: MD 15.30 mmHg, 95% CI 7.48 to 23.12, P < 0.001, I^2 = 44%; 2 studies, 120 participants; Analysis 1.7). 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 (diuretics: MD 10.85 mmHg, 95% CI 7.92 to 13.78; P < 0.001, I^2 = 72%; 4 studies, 411 participants; other drug classes: MD 7.40 mmHg, 95% CI 3.10 to 11.70; P <0.001; 1 study, 356 participants; test for subgroup differences P = 0.19; Analysis 1.8).

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). Pooled data showed that discontinuation of antihypertensives may increase DBP compared to continuation (MD 3.50 mmHg, 95% CI 1.82 to 5.18; P < 0.001, I^2 = 47%; 5 studies, 768 participants; low certainty of evidence; Analysis 1.9). Moderate heterogeneity was found (I^2 = 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. There was a difference between the studies with a follow-up of < 12 months compared to ≥ 12 months (MD 2.68 mmHg, 95% CI 0.87 to 4.49; P = 0.004, I^2 = 0%; 3 studies, 646 participants; and MD 8.70 mmHg, 95% CI 4.15 to 13.25; P < 0.001, I^2 = 0%; 2 studies, 122 participants; respectively, test for subgroup differences P < 0.001; Analysis 1.10). Subgroup analysis by type of antihypertensive drug didn't explain the heterogeneity and there was no difference between these subgroups (diuretics: MD 4.42 mmHg, 95% CI 2.03 to 6.81; P = 0.09, I^2 = 53%; 4 studies, 412 participants; other drug classes: MD 2.60 mmHg, 95% CI 0.24 to 4.96; P 0.03; 1 study, 356 participants; test for subgroup differences P = 0.29; Analysis 1.11).

Falls

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

Quality of life (QoL)

One study (N =356, participants with mild cognitive defects) reported change in 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). Discontinuation may result in little to no difference in change in QoL (MD −0.10, 95% CI −0.35 to 0.15; P = 0.43; 1 study, 356 participants; low certainty of evidence; Analysis 1.12). It was determined that there was low certainty of evidence for this outcome due to risk of bias and small sample size (single study).

Success (rate) of withdrawal from antihypertensive drugs

Four studies reported the success of withdrawal as measured by remaining off the medication. Three studies (Maland 1983; Myers 1982; Walma 1997) were included in the meta-analysis which found that discontinuation may increase the risk of experiencing raised blood pressure or other clinical criteria (as pre-defined by the studies) that would require restarting of therapy/removal from the study (OR 3.23, 95% CI 1.86 to 5.61, P < 0.001, I^2 = 71%; 3 studies, 341 participants; low certainty of evidence; Analysis 1.13). 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 BP before treatment than those who didn't. 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 myocardial infarction, 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.

Discussion

Summary of main results

This review update did not identify any new studies for inclusion. Despite this, reporting this update was important to show that there were no new eligible studies and put the findings into the current context, including knowledge from recent studies not eligible for inclusion in our review to inform future research directions.

Our systematic review identified six RCTs on antihypertensive discontinuation in older people. See Summary of findings table 1. Based on currently available evidence, discontinuation of antihypertensives (for hypertension or primary prevention of CVD in older adults) may have little to no effect on all-cause mortality or stroke compared with continuation and the evidence is very uncertain about the effect of discontinuing antihypertensives on myocardial infarction. 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 difference. Therefore, additional studies may change these results. The evidence is very uncertain about the effect of antihypertensive discontinuation on the risk of adverse drug reactions; eligible studies did not assess adverse drug *withdrawal* reactions specifically and, in general, all reporting of adverse drug reactions 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. Antihypertensive discontinuation may result in little to no difference in hospitalisations (low certainty of evidence); however, this outcome was only assessed in one study. We did find evidence surrounding the effect of discontinuation on BP, however, again the certainty of evidence is low. Discontinuation may lead to an increase in both SBP and DBP compared to continuation, though there was heterogeneity in these estimates which could not be fully explained. No studies were identified which reported falls.

Overall, there was limited available evidence describing the effect of antihypertensive discontinuation on clinically-important outcomes such as mortality or cardiovascular events in older people. However, discontinuation may lead to an increase in BP.

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 BP. 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 at risk of, or currently suffering from harm such as falls. Additionally, there was significant variability in the inclusion and exclusion criteria as to what they defined controlled BP 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 may limit the applicability of our findings. In usual care, after discontinuation, BP can be monitored and the medication would be restarted if the BP 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). A lack of information about tapering has important implications as the process of medication withdrawal may have an impact on adverse effects. Tapering would likely be conducted in clinical practice to determine the lowest effective dose of the medication and minimise adverse drug withdrawal events (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-pharmacological 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; Sheppard 2023).

The sample sizes of the studies were generally small. Additionally, 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, the number of events was low and the confidence intervals crossed both the null and a clinically important magnitude, so 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.

In addition to the above limitations based on the studies that fulfilled our inclusion/exclusion criteria, our methods did result in exclusion of studies that could also be applicable to practice. Firstly, in ideal clinical practice, discontinuation of antihypertensive medications would be a result of shared decision-making (Scott 2019; Sawan 2022). Secondly, this systematic review was focused on antihypertensive medication used for hypertension or primary prevention of cardiovascular disease. As such, we excluded studies where >20% of participants had any history of CVD. However, the majority of older adults, especially those with multimorbidity, polypharmacy and frailty do have some history of CVD (Dunlay 2016); as such studies being conducted now (e.g. OPTiMISE) are focusing on participants without a recent history of CVD. Thirdly, we only included studies where all antihypertensive medications were ceased (with the intent of reducing confounding of the findings). However, many older adults are on multiple antihypertensive medications, and it would not be clinically appropriate to cease all their medications simultaneously or in rapid succession. Pragmatic interventions which involve gradual tapering of one medication at a time with monitoring of BP and clinical benefits and harms, better reflect clinical practice (such as the approach in Sheppard 2020 and Kraut 2022). As such, future reviews/updates on this topic may consider expanding the inclusion/exclusion criteria to address these limitations to maximise the clinical relevance of the findings.

Overall, with the current evidence, it is very difficult to establish the risk:benefit balance on withdrawal of antihypertensive medications. This may contribute to limited translation of evidence into practice, particularly through the lack of inclusion of deprescribing recommendations in clinical practice 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'. However, their 2023 update (Mancia 2023) includes the recommendation: 'Reduction of treatment can be considered in patients age 80 years or older with a low SBP (<120mmHg) or in the presence of severe orthostatic hypotension or a high frailty level'. The guideline still notes that deprescribing (when indicated) should be conducted cautiously due to a lack of data on the process and outcomes. Withdrawal of antihypertensives is not mentioned in the UK NICE guideline [NG136], updated 2022 (NICE 2022), or in the International Society of Hypertension Global Hypertension Practice Guidelines (Unger 2020), which target high, low and middle-income countries. A growing number of guidelines acknowledge the need for separate blood pressure targets for older adults, multimorbidity and frailty (Bogaerts 2022).

Factors that are likely relevant to decision making that were not able to be explored in this review include populations at different levels of risk, individual patient goals of care, and prioritisation of resources. Individuals with a greater risk of harm from medication use include those experiencing an adverse drug reaction (e.g. falls), and those with frailty, dementia and polypharmacy. Considering deprescribing of antihypertensives may also be relevant to patients with limited life expectancy whose goals of care have shifted from prolonging life to optimising quality of life, especially when they are experiencing medication burden or difficulties swallowing. Deprescribing of antihypertensives requires resources to determine suitability of withdrawal, including discussions with patients and families, and to conduct and monitor the withdrawal. Therefore, clinicians may need to prioritise resources to the most pressing areas of need, which may include deprescribing of other higher risk medications. 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; Sawan 2021; Weir 2022; Sheppard 2022).

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.

Concerns around imprecision were due to the total number of events being low and wide 95% CIs that included both the null effect and what would be considered an appreciable effect (for example, for the outcomes mortality, myocardial infarction, hospitalisation and stroke). The age of the studies and knowledge that standards of care have changed since the studies were completed was the main consideration when downgrading for indirectness (particularly for mortality and stroke). Finally, inconsistency due to the heterogeneity which mostly couldn't be explained by our subgroup analyses was a reason for downgrading for BP.

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 recent concept. As such, data on the feasibility and outcomes in early studies were poorly reported. For this update, we updated our search strategy using a recently developed and validated search strategy for deprescribing (Morel 2022). However, the developers of this search strategy highlight that further research is needed to evaluate its effectiveness prospectively for systematic reviews. Additionally, it is possible that early studies reporting deprescribing results may not have used these terms. Therefore, our search strategy may not have identified all relevant studies.

Few studies overall were included in this review, and no new studies were identified in this update; 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.

Furthermore, to maximise the number of potentially eligible studies, we defined 'older' participants as those aged 50 years or older. This may not adequately reflect the population of older adults in the present day, where many people live well into their eighties and nineties. This definition also resulted in the inclusion of some studies which enrolled younger patients (Langford 1984), which may partly explain the low event rates observed in this review for the primary outcomes of interest.

Finally, the search of this update was conducted in October/November 2022 (>12 months ago). Given that no new studies were identified in this update, and based on the knowledge of the authors and lack of ongoing potentially eligible studies, we do not anticipate that updating the search now would identify any new eligible studies. See also in Overall completeness and applicability of evidence, that based on finding no new studies in this update and the limitations of the current methods, future efforts to update this review would be best directed to altered inclusion/exclusion criteria to best inform practice.

Agreements and disagreements with other studies or reviews

This is an update of the first systematic review and meta-analysis to investigate the effect of withdrawal of antihypertensive medications in older people on multiple outcome measures including mortality, myocardial infarction and adverse drug withdrawal events and investigate the success of withdrawal. 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 BP and, less commonly, heart failure. Similar reasons for restarting antihypertensive medications were identified in our review (BP 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).

Since the original publication of this review, two new trials have been published examining the effects of antihypertensive medication withdrawal on clinical outcomes (OPTIMISE [Sheppard 2023] and DANTON [Bogaerts 2022]), but these could not be included due to not meeting our study inclusion criteria. The OPTiMISE trial examined the effects of withdrawing one antihypertensive medication in patients aged ≥80 years, with SBP <150 mmHg at baseline and prescribed two or more antihypertensive medications. In 569 participants enrolled to the study, two thirds of those randomised to the intervention group were able to maintain medication reduction throughout 12 week follow-up, and there was no difference between groups in the proportion of patients with controlled BP. The rate of serious adverse events (leading to hospitalisation or death) was very low and so once again there was insufficient evidence to determine the effects of antihypertensive medication withdrawal on mortality and cardiovascular disease outcomes. The DANTON study enrolled 205 participants from nursing homes in the Netherlands with the aim of examining whether antihypertensive deprescribing reduces neuropsychiatric symptoms and improves quality of life. After two years of recruitment, less than half of the planned sample size had been enrolled and participants had experienced 63 serious adverse events, and the trial was stopped early due to futility (Bogaerts 2022).

A systematic review published between our original review and this update aimed to examine the benefit-risk profile of deprescribing antihypertensives (Crisafulli 2021). This review included people of any age taking antihypertensives for primary or secondary prevention. They included 5 studies (only one of our included studies was included in their review, Maland 1983), including the OPTiMISE study described above. They concluded that their findings support the NICE guideline, 'Multimorbidity: clinical assessment and management' (NICE 2016) which discusses that stopping preventive medications, such as antihypertensives, could result in benefits in specific populations of people with multimorbidity (e.g. frailty).

All of these trials and reviews (with the exception of the DANTON study [Bogaerts 2022]) concluded that deprescribing of antihypertensive medications is likely feasible in a proportion of older adults, although the proportion in which it is likely to be successful varies. However, there remains uncertainty in the likely benefit and potential harms of antihypertensive withdrawal.

Authors' conclusions

Implications for practice

The evidence suggests that there is little to no effect of withdrawal of antihypertensive drugs used for hypertension or primary prevention of CVD in older adults on the clinical outcomes mortality, hospitalisation and stroke. The effect on myocardial infarction and adverse drug reactions including adverse drug withdrawal events is very uncertain. Withdrawal of antihypertensives may lead to an increase in both SBP and DBP. No studies reported on the outcome of falls.

The limitations of the available data on deprescribing of antihypertensives, as described in the discussion, limit 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. In included trials, there was an absence of data on adverse events, as well as information about the process of drug withdrawal (tapering) which can influence adverse events, limiting application of findings to practice.

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 finding that a majority of participants in the discontinuation group do not need to restart the medication indicates feasibility of withdrawal and that the evidence suggests that there is little to no difference in clinical outcomes (with recognition of the uncertainty of these findings), may help clinicians when considering deprescribing antihypertensives and discussing this with patients.

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 clinical outcomes 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. Given guidelines commonly advocate the use of multiple drug combinations to manage hypertension, future 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 - either within or between classes of medication.

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 harms of antihypertensive discontinuation exist between specific populations. It is noted that clinical guidance in terms of hypertension treatment initiation has different thresholds according to the age of the patient (NICE 2022), and, as such, it would be important to establish if the blood pressure thresholds for possible deprescribing should also vary according to age. It will also be useful for future studies to clearly describe their discontinuation plan (e.g. tapering rate, duration and monitoring), 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. Such trials are currently being undertaken, but will take a few years to report their findings (Sheppard 2022). Until these data are available, the long term benefits and harms of antihypertensive deprescribing remain unknown.

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 (Moriarty 2022). 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. 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; Gnjidic 2022).

Based on not identifying any new studies to include in this update, and the reasons why several studies (which have clinical relevance) were excluded, future updates may benefit from altering the inclusion/exclusion criteria. Specifically, a future update of this review may only exclude studies with participants with a recent (e.g. <12 months) history of CVD, and include more pragmatic approaches to deprescribing (e.g. including shared decision making, tapering of antihypertensives one medication at a time), so that the findings are more widely applicable to real world population and practice.

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The authors would also like to acknowledge Professor Zaheer-Ud-Din Babar, who led the development of the protocol for this review, Christine Y Lu who co-authored the protocol (Babar 2017), and Todd M Gammie who contributed to the previous version of this review (Reeve 2020).

Cochrane Hypertension supported the authors in the development of this review.

The following people conducted the editorial process for this article:

• Sign-off Editor (final editorial decision): Juan Erviti, Ph.D. Navarre Health Service, Unit of Innovation and Organization, Pamplona, Spain

• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Ben Ridley, Central Editorial Service

• Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jacob Hester, Central Editorial Service

• Copy Editor (copy editing and production): [NAME, AFFILIATION];

• Peer-reviewers (provided comments and recommended an editorial decision): Dr Anneka Mitchell, Pharmacy Department, University Hospitals Plymouth NHS Trust, UK (clinical/content review), Brian Duncan (consumer review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Steve McDonald, Cochrane Australia (search review). 1 additional peer reviewers provided [CLINICAL/CONTENT] peer review but chose not to be publicly acknowledged.

Data and analyses

Comparison 1

Discontinuation by no treatment/placebo of antihypertensives vs Continuation

Outcome or subgroup title	No. of studies	No. of participants	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 participants	Statistical method	Effect size
1.3 Myocardial infarction (fatal and nonfatal)	2	447	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.86 [0.19, 17.98]
1.4 Hospitalisation	1	385	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.33, 2.10]
1.5 Stroke (fatal + nonfatal + TIA)	3	524	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.25, 8.35]
1.6 Systolic blood pressure	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.7 Systolic blood pressure subgrouped on duration	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.7.1 Less than 12 months	3	647	Mean Difference (IV, Fixed, 95% CI)	9.17 [6.62, 11.71]
1.7.2 12 months or longer	2	120	Mean Difference (IV, Fixed, 95% CI)	15.30 [7.48, 23.12]
1.8 Systolic blood pressure subgrouped on drug type	5	767	Mean Difference (IV, Fixed, 95% CI)	9.75 [7.33, 12.18]
1.8.1 Diuretics	4	411	Mean Difference (IV, Fixed, 95% CI)	10.85 [7.92, 13.78]
1.8.2 Other	1	356	Mean Difference (IV, Fixed, 95% CI)	7.40 [3.10, 11.70]
1.9 Diastolic blood pressure	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.10 Diastolic blood pressure subgrouped on duration	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.10.1 Less than 12 months	3	646	Mean Difference (IV, Fixed, 95% CI)	2.68 [0.87, 4.49]
1.10.2 12 months or longer	2	122	Mean Difference (IV, Fixed, 95% CI)	8.70 [4.15, 13.25]
1.11 Diastolic blood pressure subgrouped on drug type	5	768	Mean Difference (IV, Fixed, 95% CI)	3.50 [1.82, 5.18]
1.11.1 Diuretics	4	412	Mean Difference (IV, Fixed, 95% CI)	4.42 [2.03, 6.81]
1.11.2 Other	1	356	Mean Difference (IV, Fixed, 95% CI)	2.60 [0.24, 4.96]
1.12 Quality of life	1	356	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.35, 0.15]
1.13 Sucess rate - withdrawal/resumption due to hypertension or other clinical reason	3	341	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.23 [1.86, 5.61]

What's new

Date	Event	Description
6 November 2024	New citation required but conclusions have not changed	Background and discussion and conclusions were updated.
6 November 2024	New search has been performed	Author changes: Aili Langford and James Sheppard have been added as review authors. Todd Gammie has been removed. New database searches were conducted for this update (i.e. the search conducted in 2022); no new studies identified for inclusion.

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

All authors contributed to the planning of this review update.

Danijela Gnjidic, Aili Langford, Mouna Sawan, Wade Thompson and Emily Reeve screened abstracts and full texts for this update. Danijela Gnjidic, Aili Langford, Vanessa Jordan, James Sheppard, Adam Todd, Ingrid Hopper, Sarah Hilmer and Emily Reeve, revised and contributed to the new text of this update.

All authors reviewed and revised the manuscript.

Some authors involved in the protocol (Babar 2017) and the previous published version of this review in Reeve 2020 are no longer included on the author byline: ZUD Babar, CY Lu and TM Gammie. Some of the content retained in this review reflects their contributions.

Declarations of interest

Danijela Gnjidic: Nothing to declare

Aili Langford: is an Executive Committee member of the Australian Deprescribing Network (ADeN).

Vanessa Jordan: Vanessa Jordan is a sign off editor for Cochrane and a methodology editor for the Cochrane Gynaecology and Fertility Group. However, she was not involved in the editorial process for this article.

Mouna Sawan: Nothing to declare

James Sheppard: has received research funding from government and charity organisations to undertake trials of antihypertensive deprescribing, one of which was considered but not included in this review. James Sheppard was not involved in eligibility decisions about, extraction of data from, risk of bias or GRADE assessment of his own trial(s).

Wade Thompson: Nothing to declare

Adam Todd: Nothing to declare

Ingrid Hopper: Nothing to declare

Sarah N Hilmer: Nothing to declare

Emily Reeve: is the Chair of the Australian Deprescribing Network (ADeN) and receives royalties from UpToDate (Wolters Kluwer) for writing a chapter on deprescribing.

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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.

In the protocol we stated that we would consider all antihypertensive medications as eligible medications. Alpha-blockers and clonidine were not explicitly listed, however they were not excluded and trials of these drugs were considered in the review. For transparency, we have listed these medicines as being eligible in this update.

For this update we added the following databases to the search strategy:

- EBSCO (all databases on platform, searched 27 October 2022);
- Clarivate Web of Science (searched 27 October 2022);
- Google Scholar via Harzing's Publish or Perish (Publish or Perish 2022, searched 27 October 2022).

Additionally, we updated our search strategy using a recently developed and validated search strategy for deprescribing (Morel 2022). See Appendix 1 for updated search strategy.

Finally, for this update we revised the wording of our objective to better reflect the methods and outcomes included in the summary of findings table.

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:** Furosemide, furosemide and spironolactone, amiloride-hydrocholorthiazide combination, furosemide 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* • **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 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 • *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** 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 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. **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 **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 **Address:** Dr Lawrence J Lutz, MD, MSCM, Department of Family and Community Medicine, University of Utah, Salt Lake City, Utak 84132
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
Other bias	Low risk	Judgement comment: no other areas of concern

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 participants with diabetes mellitus or those who had 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 **Authors name:** Justine E. F. Moonen **Institution:** Department of Psychiatry, Leiden University Medical Centre **Email:** j.e.f.moonen@lumc.nl **Address:** Department of Psychiatry, Leiden University Medical Center, PO Box 10392, 2300 WB, Leiden, the Netherlands
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	
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, furosemide, spironolactone, hydrochlorothiazide and spironolactone, hydrochlorothiazide and triamterene). 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 **Antihypertensives taken:** hydrochlorothiazide - 18/14 (continue/stop); furosemide - 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
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

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%) • *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 furosemide 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 furosemide 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 furosemide 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:** furosemide (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 **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	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)."

bias) All outcomes		
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).
ACTRN12622000329763 2022	Wrong intervention
Aharaz 2021	Wrong intervention
Andersen 2008	Wrong patient population
Andersen 2009	Wrong patient population
Applegate 2020	Wrong study design
Azizi 2020	Wrong intervention
Balsom 2020	Wrong intervention
Band 2016	Wrong intervention
Bauer 2021	Wrong patient population
Bawazeer 2022	Wrong intervention
Bayliss 2022	Wrong intervention
Beer 2011	Wrong intervention
Blaufox 1984	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives).
Blom 1993	Wrong intervention
Bogaerts 2022	Wrong patient population
Bonnet-Zamponi 2013	Wrong intervention
Bosch 2021	Wrong study design
Bovee 2020	Wrong intervention
Boye 2017	Wrong intervention
Cateau 2021	Wrong intervention
Cohen 2021	Wrong intervention
Crisafulli 2021	Wrong study design
CTRI/2021/01/030199 2021	Wrong intervention
Curtin 2020	Wrong intervention
Ekbom 1992	Wrong study design
ENOS Trial Investigators 2015	Wrong intervention
Gulla 2018	Wrong intervention
Guthrie 2002	

Study	Reason for exclusion
	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
Hung 2014	Wrong study design
Jondeau 2009	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives)
Juraschek 2022	One or both groups had confounding treatment (such as additional dietary or exercise intervention or other antihypertensives)
Kraut 2022	Wrong intervention
Kua 2021	Wrong intervention
Langford 1985	Wrong patient population
Lewin 2012	Wrong patient population
Luymes 2018	Wrong patient population
Manning 2015	Wrong intervention
McDonald 2022	Wrong intervention
Medical Research Council Working Party 1986	Wrong patient population
Morgan 1994	Wrong study design
Morselli 2022	Wrong study design
NCT00219063 2005	Wrong patient population
NCT00785512 2008	Clinical trial registry citation (of an ineligible study due to wrong patient population)
NCT05307666 2022	Wrong intervention
NCT05585268 2022	Wrong intervention
Nelson 2003	Wrong study design
Neusy 1989	Wrong intervention
NHF 1981	Wrong intervention
Ohkuma 2022	Wrong intervention
Pazan 2018	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)
Potter 2016	Wrong intervention
Ramirez-Jimenez 2018	Wrong intervention
Ramirez-Jimenez 2021	Wrong intervention
Robinson 2010	Wrong intervention
Ruoff 1986	Wrong population as not older adults; half of participants < 50 years
Sharma 2022	Wrong intervention
Sheppard 2020	Wrong intervention
Stange 2013	Wrong intervention
Szam 1981	Wrong study design
Vaur 1998	Wrong intervention
Veterans Administration Cooperative 1975	Wrong patient population
Wachtell 2022	Wrong study design
Xu 2017	Wrong intervention
Yang 2021	Wrong intervention
Zhang 2019	Wrong study design

Appendices

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) ALL <1946 to October 26, 2022>
Search Date: 27 October 2022

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1 exp aged/
2 exp geriatrics/
3 geriatric*.hw.
4 health services for the aged/
5 middle aged/
6 (advanced years or ageing or aging or community-dwelling or dementia or older* 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 citizen*).tw,kf.
7 (old* adj3 (adult? or female? or male? or men or patient* or people or person* or population* or resident* or women)).tw,kf.
8 ((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.
9 (quinquagenarian* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian* or centenarian* or supercentenarian*).tw,kf.
10 (aged or aging or ageing or elder* or geriatric* or gerontolog*).jw,nw.
11 or/1-10
12 hypertension/
13 essential hypertension/
14 hypertens*.tw,kf.
15 ((elevat* or high or increas* or lower* or rais* or rise or rising or rose) adj2 (arterial pressur* or blood pressur* or diastolic pressur* or systolic pressur*)).tw,kf.
16 ((elevat* or high or increas* or lower* or rais* or rise or rising or rose) adj2 (bp or dbp or sbp)).tw,kf.
17 or/12-16
18 exp antihypertensive agents/
19 antihypertens*.tw,kf.
20 hypertension/dt
21 essential hypertension/dt
22 or/18-21
23 exp thiazides/
24 exp diuretics/
25 exp sodium chloride symporter inhibitors/
26 exp sodium potassium chloride symporter inhibitors/
27 thiazide?.tw,kf.
28 diuretic?.tw,kf.
29 ((sodium chloride adj2 cotransporter inhibit*) or (sodium chloride adj2 co-transporter inhibit*) or (sodium chloride adj2 symporter inhibit*)).tw,kf.
30 (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).tw,kf.
31 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw,kf.
32 or/23-31
33 exp angiotensin-converting enzyme inhibitors/
34 ((angiotensin converting enzyme adj2 antagonist?) or (angiotensin I-converting enzyme adj2 antagonist?)).tw,kf.
35 ((angiotensin converting enzyme adj2 inhibit*) or (angiotensin I-converting enzyme adj2 inhibit*)).tw,kf.
36 (ace adj2 inhibit*).tw,kf.
37 (acei or aceis).tw,kf.
38 (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.
39 or/33-38
40 exp angiotensin receptor antagonists/
41 (angiotensin adj3 receptor antagon*).tw,kf.
42 (angiotensin adj3 receptor block*).tw,kf.
43 (arb or arbs).tw,kf.
44 (sartan or sartans).tw,kf.
45 (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.
46 or/40-45
47 exp calcium channel blockers/
48 ((calcium adj2 antagonist?) or (calcium adj2 block*) or (calcium adj3 inhibit*)).tw,kf.
49 (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.
50 or/47-49
51 exp adrenergic beta-antagonists/
52 ((beta adj2 adrenergic?) or (beta adj2 antagonist?)).tw,kf.
53 ((beta adj2 block*) or (beta adj2 receptor?)).tw,kf.
54 (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.
55 or/51-54
56 exp adrenergic alpha antagonists/
57 ((adrenergic adj2 alpha) or (adrenergic adj2 antagonist?)).tw,kf.
58 ((adrenergic adj2 block*) or (alpha adj2 block*) or (receptor? adj2 block*)).tw,kf.
59 (alpha adj2 receptor antagonist?).tw,kf.
60 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw,kf.
61 or/56-60
62 22 or 32 or 39 or 46 or 50 or 55 or 61
63 deprescriptions/
64 (deprescri* or de-prescri*).tw,kf.
65 polypharmacy/
66 (polymedic* or polypharm*).tw,kf.
67 inappropriate prescribing/
68 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 drug*).tw,kf.
69 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 medica*).tw,kf.
70 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 pharmaceut*).tw,kf.
71 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 prescri*).tw,kf.
72 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 therap*).tw,kf.
73 (misprescri* or mis-prescri* or overprescri* or over-prescri*).tw,kf.
74 medication review/
75 ((drug utili* or medication*) adj2 review*).tw,kf.
76 withholding treatment/
77 substance withdrawal syndrome/
78 discontinu*.tw,kf.
79 (reduc* adj4 (antihypertens* or anti-hypertens* or dosage? or dose or doses or drug* or medicat* or polypharm* or prescri*)).tw,kf.
80 (stop? or stopped or stopping).tw,kf.
81 taper*.tw,kf.
82 (withdraw* or withdrew).tw,kf.
83 (withheld or withhold*).tw,kf.
84 or/63-83
85 randomized controlled trial.pt.
86 controlled clinical trial.pt.
87 randomi*ed.tw.
88 placebo.ab.
89 clinical trials as topic/
90 randomly.ab.
91 trial.ti.
92 or/85-91
93 animals/ not (humans/ and animals/)
94 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/
95 (eclamp* or pregnancy-induced or intraocular hypertens* or ocular hypertens* or preeclamp* or pre-eclamp*).ti.
96 92 not (93 or 94 or 95)
97 11 and 17 and 62 and 84 and 96

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies
Search Date: 24 November 2022

#1 (ceased OR ceasing OR cessation OR deprescri* OR discontinu* OR error* OR inappropriate* OR stop* OR taper* OR withdraw* OR withdrew OR withheld OR withhold*) AND INREGISTER
#2 (#9 AND #10 AND #14)

#3 (RCT:DE OR Review:ODE) AND INREGISTER
#4 #15 AND #16
#5 (advanced years OR ageing OR aging OR community-dwelling OR dementia OR older* OR elderly OR frail OR geriatric* OR gerontolog* OR "later life" OR "middle age" OR "middle age" OR midlife OR "nursing care" OR "nursing home" OR "nursing homes" OR "old age" OR "oldest old" OR pensioner* OR post-menopausal OR postmenopausal OR "senior citizen" OR "senior citizens") AND INREGISTER
#6 ((old*) NEAR3 (adult* OR female* OR male* OR men OR patient* OR people OR person* OR population* OR resident* OR women)) AND INREGISTER
#7 ((old OR older OR years) NEAR2 (49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58)) AND INREGISTER
#8 ((old OR older OR years) NEAR2 (59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68)) AND INREGISTER
#9 ((old OR older OR years) NEAR2 (69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78)) AND INREGISTER
#10 ((old OR older OR years) NEAR2 (79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88)) AND INREGISTER
#11 ((old OR older OR years) NEAR2 (89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100)) AND INREGISTER
#12 (quinquagenarian* OR sexagenarian* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*) AND INREGISTER
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#14 (antihypertens* OR hypertens*) AND INREGISTER
#15 ((elevat* OR high OR increas* OR lower* OR rais* OR rise OR rising OR rose) NEAR2 ("arterial pressure" OR "blood pressure" OR "diastolic pressure" OR "systolic pressure")) AND INREGISTER
#16 ((elevat* OR high OR increas* OR lower* OR rais* OR rise OR rising OR rose) NEAR2 (bp OR dbp OR sbp)) AND INREGISTER
#17 (#10 OR #11 OR #12)
#18 (ceased OR ceasing OR cessation OR deprescri* OR discontinu* OR error* OR inappropriate* OR stop* OR taper* OR withdraw* OR withdrew OR withheld OR withhold*) AND INREGISTER
#19 (#9 AND #10 AND #14)
#20 (RCT:DE OR Review:ODE) AND INREGISTER
#21 #15 AND #16

Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies
Search Date: 29 October 2022

#1 (advanced years OR ageing OR aging OR community-dwelling OR dementia OR older* OR elderly OR frail OR geriatric* OR gerontolog* OR "later life" OR "middle age" OR "middle age" OR midlife OR "nursing care" OR "nursing home" OR "nursing homes" OR "old age" OR "oldest old" OR pensioner* OR post-menopausal OR postmenopausal OR "senior citizen" OR "senior citizens") AND CENTRAL:TARGET
#2 ((old*) NEAR3 (adult* OR female* OR male* OR men OR patient* OR people OR person* OR population* OR resident* OR women)) AND CENTRAL:TARGET
#3 ((old OR older OR years) NEAR2 (49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58)) AND CENTRAL:TARGET
#4 ((old OR older OR years) NEAR2 (59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68)) AND CENTRAL:TARGET
#5 ((old OR older OR years) NEAR2 (69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78)) AND CENTRAL:TARGET
#6 ((old OR older OR years) NEAR2 (79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88)) AND CENTRAL:TARGET
#7 ((old OR older OR years) NEAR2 (89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100)) AND CENTRAL:TARGET
#8 (quinquagenarian* OR sexagenarian* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*) AND CENTRAL:TARGET
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 (antihypertens* OR hypertens*) AND CENTRAL:TARGET
#11 ((elevat* OR high OR increas* OR lower* OR rais* OR rise OR rising OR rose) NEAR2 ("arterial pressure" OR "blood pressure" OR "diastolic pressure" OR "systolic pressure")) AND CENTRAL:TARGET
#12 ((elevat* OR high OR increas* OR lower* OR rais* OR rise OR rising OR rose) NEAR2 (bp OR dbp OR sbp)) AND CENTRAL:TARGET
#13 (#10 OR #11 OR #12)
#14 (ceased OR ceasing OR cessation OR deprescri* OR discontinu* OR error* OR inappropriate* OR stop* OR taper* OR withdraw* OR withdrew OR withheld OR withhold*) AND CENTRAL:TARGET
#15 (#9 AND #10 AND #14)

Database: Embase <1974 to 2022 October 26>
Search Date: 27 October 2022

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1 exp aged/
2 exp geriatrics/
3 geriatric*.hw.
4 exp elderly care/
5 middle aged/
6 (advanced years or ageing or aging or community-dwelling or dementia or older* 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 citizen*).tw,kf.
7 (old* adj3 (adult? or female? or male? or men or patient* or people or person* or population* or resident* or women)).tw,kf.
8 ((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.
9 (quinquagenarian* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian* or centenarian* or supercentenarian*).tw,kf.
10 (aged or aging or ageing or elder* or geriatric* or gerontolog*).jx.
11 or/1-10
12 exp hypertension/
13 hypertens*.tw.
14 ((elevat* or high or increas* or lower* or rais* or rise or rising or rose) adj2 (arterial pressur* or blood pressur* or diastolic pressur* or systolic pressur*)).tw,kf.
15 ((elevat* or high or increas* or lower* or rais* or rise or rising or rose) adj2 (bp or dbp or sbp)).tw,kf.
16 or/12-15
17 exp *antihypertensive agent/
18 antihypertens*.tw,kf.
19 hypertension/dt
20 or/17-19
21 exp *diuretic agent/
22 exp *thiazide diuretic agent/
23 exp *loop diuretic agent/
24 thiazide?.tw,kf.
25 diuretic?.tw,kf.
26 ((sodium chloride adj2 cotransporter inhibit*) or (sodium chloride adj2 co-transporter inhibit*) or (sodium chloride adj2 symporter inhibit*)).tw,kf.
27 (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).tw,kf.
28 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw,kf.
29 or/21-28
30 exp *dipeptidyl carboxypeptidase inhibitor/
31 ((angiotensin converting enzyme adj2 antagonist?) or (angiotensin I-converting enzyme adj2 antagonist?)).tw,kf.
32 ((angiotensin converting enzyme adj2 inhibit*) or (angiotensin I-converting enzyme adj2 inhibit*)).tw,kf.
33 (ace adj2 inhibit*).tw,kf.
34 (acei or aceis).tw,kf.
35 (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.
36 or/30-35
37 exp *angiotensin receptor antagonist/
38 (angiotensin adj3 receptor antagon*).tw,kf.
39 (angiotensin adj3 receptor block*).tw,kf.
40 (arb or arbs).tw,kf.
41 (sartan or sartans).tw,kf.
42 (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.
43 or/37-42
44 exp *calcium channel blocking agent/
45 ((calcium adj2 antagonist?) or (calcium adj2 block*) or (calcium adj3 inhibit*)).tw,kf.
46 (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.
47 or/44-46
48 exp *beta adrenergic receptor blocking agent/
49 ((beta adj2 adrenergic?) or (beta adj2 antagonist?)).tw,kf.
50 ((beta adj2 block*) or (beta adj2 receptor?)).tw,kf.
51 (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.
52 or/48-51
53 exp *alpha adrenergic receptor blocking agent/
54 ((adrenergic adj2 alpha) or (adrenergic adj2 antagonist?)).tw,kf.
55 ((adrenergic adj2 block*) or (alpha adj2 block*) or (receptor? adj2 block*)).tw,kf.
56 (alpha adj2 receptor antagonist?).tw,kf.
57 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw,kf. (
58 or/53-57
59 20 or 29 or 36 or 43 or 47 or 52 or 58
60 deprescription/
61 (deprescri* or de-prescri*).tw,kf.
62 exp polypharmacy/
63 (polymedic* or polypharm*).tw,kf.
64 exp prescribing error/ (3083)
65 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 drug*).tw,kf.
66 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 medica*).tw,kf.
67 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 pharmaceut*).tw,kf.
68 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 prescri*).tw,kf.
69 ((cease* or cessation or error* or inappropriat* or incorrect* or problem or problematic or unnecessary) adj3 therap*).tw,kf.
70 (misprescri* or mis-prescri* or overprescri* or over-prescri*).tw,kf.
71 "drug utilization review"/
72 ((drug utili* or medication*) adj2 review*).tw,kf.
73 exp *treatment withdrawal/
74 withdrawal syndrome/
75 discontinu*.tw,kf.
76 (reduc* adj4 (antihypertens* or anti-hypertens* or dosage? or dose or doses or drug* or medicat* or polypharm* or prescri*)).tw,kf.
77 (stop? or stopped or stopping).tw,kf.
78 taper*.tw,kf.
79 (withdraw* or withdrew).tw,kf.
80 (withheld or withhold*).tw,kf.
81 or/60-80
82 randomized controlled trial/
83 crossover procedure/
84 double-blind procedure/
85 (randomi?ed or randomly).tw.
86 (crossover* or cross-over*).tw.
87 placebo.ab.
88 (doubl* adj blind*).tw.
89 assign*.ab.
90 allocat*.ab.
91 or/82-90
92 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
93 exp pregnancy/ or exp pregnancy complication/ or intraocular hypertension/
94 (eclamp* or pregnancy-induced or intraocular hypertens* or ocular hypertens* or preeclamp* or pre-eclamp*).ti.

95 91 not (92 or 93 or 94)
96 11 and 16 and 59 and 81 and 95

Database: EBSCO (All EBSCO databases available via University of British Columbia Library)
Search Date: 27 October 2022

((advanced years OR ageing OR aging OR community-dwelling OR dementia OR older* 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 older OR oldest old OR pensioner* OR post-menopausal OR postmenopausal OR senior citizen* OR quinquagenarian* OR sexagenarian* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*)) AND ((antihypertens* OR elevated blood pressure OR high blood pressure OR hypertens*)) AND TI ((cease* OR ceasing OR deprescri* OR de-prescri* OR discontinu* OR polypharm* OR stopped OR stopping OR taper* OR withdr*)) AND ((allocated OR allocation OR assigned OR controlled trial OR double-blind* OR groups OR placebo* OR randomi* OR randomly))

Databases: Clarivate Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1900-present, Conference Proceedings Citation Index- Science (CPCI-S) 1990-present, Emerging Sources Citation Index (ESCI) 2015-present
Search Date: 27 October 2022

(advanced years OR ageing OR aging OR community-dwelling OR dementia OR older* 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 older OR oldest old OR pensioner* OR post-menopausal OR postmenopausal OR senior citizen* OR quinquagenarian* OR sexagenarian* OR septuagenarian* OR octogenarian* OR nonagenarian* OR centenarian* OR supercentenarian*) (Topic) and (antihypertens* OR elevated blood pressure OR high blood pressure OR hypertens*) (Topic) and (cease* OR ceasing OR deprescri* OR de-prescri* OR discontinu* OR polypharm* OR stopped OR stopping OR taper* OR withdr*) (Title) and (allocated OR allocation OR assigned OR controlled trial OR double-blind* OR groups OR placebo* OR randomi* OR randomly) (Topic)

Database: Google Scholar via Herzing's Publish or Perish (first 200)
Search Date: 27 October 2022

Title: deprescribing
Keywords: hypertension AND randomized AND controlled AND trial

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Database: ClinicalTrials.gov Search Date: 27 October 2022 ---
Condition or disease: Hypertension
Other terms: randomized
Study Type: Interventional Studies (Clinical Trials)
Intervention/treatment: ceased OR ceasing OR cessation OR deprescri* OR discontinu* OR stop* OR taper* OR withdraw*

Database: WHO International Clinical Trials Registry Platform (ICTRP) Search Date: 28 October 2022 ---
hypertens* AND elder* AND random* AND ceas* (0)
hypertens* AND older AND random* AND ceas* (0)
hypertens* AND elder* AND random* AND deprescrib* (0)
hypertens* AND older AND random* AND deprescrib* (0)
hypertens* AND elder* AND random* AND discontinu* (1)
hypertens* AND older AND random* AND discontinu* (0)
hypertens* AND elder* AND random* AND stopp* (0)
hypertens* AND older AND random* AND stopp* (1)
hypertens* AND elder* AND random* AND taper* (0)
hypertens* AND older AND random* AND taper* (0)
hypertens* AND elder* AND random* AND withdraw* (3)
hypertens* AND older AND random* AND withdraw* (0)
hypertens* AND elder* and randomized (58)

Condition: hypertension AND Title: deprescri* (2)
Intervention: deprescri* AND Intervention: antihypertens* (3)

References

References to studies included in this review

Burr 1977 {published data only}

Burr ML, King S, Davies HE, Pathy MS. The effects of discontinuing long-term diuretic therapy in the elderly. Age and Ageing 1977;6(1):38-45. [DOI: 10.1093/ageing/6.1.38]

Langford 1984 {published data only}

* Langford HG, Blaufox MD, Oberman A, Hawkins CM, Curb JD, Cutter GR, et al. Return of hypertension after withdrawal of prolonged antihypertensive therapy, effect of weight loss, sodium reduction, and baseline factors. Transactions of the Association of American Physicians 1984;97:190-6.

Thaler L, Wassertheil-Smoller S, Blaufox MD, Oberman A, Langford HG. Effect of withdrawal of antihypertensive drug on depressive mood. American Journal of Hypertension 1993;6:1055-62.

Maland 1983 {published data only}

Maland LJ, Lutz LJ, Castle CH. Effects of withdrawing diuretic therapy on blood pressure in mild hypertension. Hypertension 1983;5:539-44.

Moonen 2015 {published data only}

* Moonen JE, Foster-Dingley JC, De Ruijter W, Van der Grond J, Bertens AS, Van Buchem MA, et al. Effect of discontinuation of antihypertensive treatment in elderly people on cognitive functioning - the DANTE study Leiden: a randomized clinical trial. JAMA Internal Medicine 2015;175:1622-30. [DOI: http://dx.doi.org/10.1001/jamainternmed.2015.4103]

Moonen JEF, Foster-Dingley JC, De Ruijter W, Van der Grond J, De Craen, AJM, Van der Mast RC. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE study Leiden. Age & Ageing 2016;45:249-55. [DOI: http://dx.doi.org/10.1093/ageing/afv199]

NTR2829. Effects of temporary discontinuation of antihypertensive treatment in older patients with cognitive impairment: a randomised controlled trial. https://www.trialregister.nl/trial/2300 (date first received 29 March 2011).

Myers 1982 {published data only}

Myers MG, Weingert ME, Fisher RH, Gryfe CI, Shulman HS. Unnecessary diuretic therapy in the elderly. Age and Ageing 1982;11(4):213-21.

Walma 1997 {published data only}

Walma EP, Hoes AW, Van Dooren C, Prins A, Van der Does E. Discontinuation of long-term diuretic therapy in the elderly: a successful and safe intervention? A randomized, placebo-controlled, double-blind trial. Huisarts en Wetenschap 1998;41(10):480-5/490.

Walma EP, Hoes AW, Van Dooren C, Prins A, Van der Does E. Withdrawal of long-term diuretic medication in elderly patients: a double blind randomised trial. BMJ (Clinical Research Ed) 1997;315(7106):464-8.

References to studies excluded from this review

Aberg 1989 {published data only}

Aberg H, Tibblin G. Addition of non-pharmacological methods of treatment in patients on antihypertensive drugs: results of previous medication, laboratory tests and life quality. Journal of Internal Medicine 1989;226(1):39-46. [DOI: 10.1111/j.1365-2796.1989.tb01351.x]

ACTRN12622000329763 2022 {published data only}

ACTRN12622000329763. Pharmacy-based screening and quality use of medicines in kidney disease. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12622000329763 (first registered 22 February 2022).

Aharaz 2021 {published data only}

Aharaz A, Rasmussen JH, McNulty HBO, Cyron A, Fabricius PK, Bengaard AK, et al. A collaborative deprescribing intervention in a subacute medical outpatient clinic: a pilot randomized controlled trial. Metabolites 2021;11(4):204. [DOI: 10.3390/metabo11040204]

Andersen 2008 {published data only}

Andersen K, Weinberger MH, Egan B, Constance CM, Ali MA, Jin J, et al. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. Journal of Hypertension 2008;26(3):589-99. [DOI: 10.1097/HJH.0b013e3282f3ad9a]

Andersen 2009 {published data only}

Andersen K, Weinberger MH, Constance CM, Ali MA, Jin J, Prescott MF, et al. Comparative effects of aliskiren-based and ramipril-based therapy on the renin system during long-term (6 months) treatment and withdrawal in patients with hypertension. Journal of the Renin-Angiotensin-Aldosterone System 2009;10(3):157-67. [DOI: http://dx.doi.org/10.1177/1470320309342407]

Applegate 2020 {published data only}

Applegate WB, Williamson JD, Berlowitz D. Deprescribing antihypertensive medication in elderly adults. JAMA 2020;324:1682. [DOI: 10.1001/jama.2020.16438]

Azizi 2020 {published data only}

* Azizi M, Daemen J, Lobo MD, Mahfoud F, Sharp ASP, Schmieder RE, et al. 12-month results from the unblinded phase of the RADIANCE-HTN SOLO trial of ultrasound renal denervation. JACC: Cardiovascular Interventions 2020;13(24):2922-33. [DOI: 10.1016/j.jcin.2021.02.014]

Rader F, Kirtane A, Wang Y, Daemen J, Lurz P, Sayer J, et al. TCT-369 durability of reduced office-measured blood pressure and antihypertensive medication use after ultrasound renal denervation: 24-month results from the RADIANCE-HTN SOLO trial. Journal of the American College of Cardiology 2021;78(19):B152. [DOI: https://doi.org/10.1016/j.jacc.2021.09.1222]

Balsom 2020 {published data only}

Balsom C, Pittman N, King R, Kelly D. Impact of a pharmacist-administered deprescribing intervention on nursing home residents: a randomized controlled trial. International Journal of Clinical Pharmacy 2020;42(4):1153-67. [DOI: 10.1007/s11096-020-01073-6]

Band 2016 {published data only}

Band R, Morton K, Stuart B, Raftery J, Bradbury K, Yao GL, et al. Home and Online Management and Evaluation of Blood Pressure (HOME BP) digital intervention for self-management of uncontrolled, essential hypertension: a protocol for the randomised controlled HOME BP trial. BMJ Open 2016;6(11):e012684. [DOI: 10.1136/bmj.m4858]

Bauer 2021 {published data only}

* Bauer A, Schreinlechner M, Sappler N, Dolejsi T, Tilg H, Aulinger BA, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. The Lancet. Respiratory medicine 2021;9(8):863-72. [DOI: 10.1016/S2213-2600(21)00362-3]

EUCTR2020-001206-35-AT. Discontinuation of ACE inhibitors in patients with COVID-19 infection. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2020-001206-35-AT (First registered 26 March 2020).

Bawazeer 2022 {published data only}

Bawazeer G, Alsaad S, Almalag H, Alqahtani A, Altulaihi N, Alodhayani A, et al. Impact of specialized clinics on medications deprescribing in older adults: a pilot study in ambulatory care clinics in a teaching hospital. Saudi Pharmaceutical Journal 2022;30(7):1027-35. [DOI: 10.1016/j.jsps.2022.04.012]

Bayliss 2022 {published data only}

Bayliss EA, Shetterly SM, Drace ML, Norton JD, Maiyani M, Gleason KS, et al. Deprescribing education vs usual care for patients with cognitive impairment and primary care clinicians: the OPTIMIZE pragmatic cluster randomized trial. JAMA Internal Medicine 2022;182(5):534-42. [DOI: 10.1001/jamainternmed.2022.0502]

Beer 2011 {published data only}

ACTRN12610000865011. Systematic Termination of Pharmaceutical Agents Trial (STOPAT): a pilot randomised trial of stopping drug therapy. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12610000865011 (first registered 15 October 2010.

* Beer C, Loh P, Peng YG, Potter K. A pilot randomized controlled trial of deprescribing. Therapeutic Advances in Drug Safety 2011;2(2):37-43. [DOI: 10.1177/2042098611400332]

Blaufox 1984 {published data only}

Blaufox MD, Langford HG, Oberman A, Hawkins CM, Wassertheil-Smoller SW, Cutter GR. Effect of dietary change on the return of hypertension after withdrawal of prolonged antihypertensive therapy (DISH). Dietary Intervention Study of Hypertension. Journal of Hypertension 1984;2(3 Suppl):S179-81. [PMID: 6599665]

Blom 1993 {published data only}

Blom MW, Sommers DK. Placebo substitution for methyldopa in geriatric hypertensive patients. South African Medical Journal (Suid-Afrikaanse Tydskrif Vir Geneeskunde) 1993;83(5):335-6. [PMID: 8211428]

Bogaerts 2022 {published and unpublished data}

* Bogaerts J, Gussekloo J, De Jong-Schmit B, Achterberg W, Poortvliet R. The DANTON study - discontinuation of antihypertensive treatment in older people with dementia living in a nursing home: results of a randomized controlled trial. Journal of Hypertension. Conference: 31st Scientific Meeting of the European Society of Hypertension, ESH 2022. Athens Greece 2022;40(Suppl 1):e1. [DOI: 10.1097/01.hjh.0000835304.61321.dc]

NTR7573. Discontinuation of antihypertensive treatment in older people with dementia living in a nursing home. http://www.who.int/trialsearch/Trial2.aspx?TrialID=NTR7573 (first registered 15 October 2018).

Bonnet-Zamponi 2013 {published data only}

Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-related readmissions to medical units of older adults discharged from acute geriatric units: results of the Optimization of Medication in AGEd multicenter randomized controlled trial. Journal of the American Geriatrics Society 2013;61(1):113-21. [DOI: 10.1111/jgs.12037]

Bosch 2021 {published data only}

Bosch J, Lonn EM, Jung H, Zhu J, Liu L, Lopez-Jaramillo P, et al. Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants. European Heart Journal 2021;42(31):2995-3007. [DOI: 10.1093/eurheartj/ehab225]

Bovee 2020 {published data only}

Bovee DM, Visser WJ, Middel I, De Mik-van Egmond A, Greupink R, Masereeuw R, et al. A randomized trial of distal diuretics versus dietary sodium restriction for hypertension in chronic kidney disease. Journal of the American Society of Nephrology 2020;31(3):650-62. [DOI: 10.1681/ASN.2019090905]

Boye 2017 {published data only}

Boyé ND, Van der Velde N, De Vries OJ, Van Lieshout EM, Hartholt KA, Mattace-Raso FU, et al. Effectiveness of medication withdrawal in older fallers: results from the improving medication prescribing to reduce risk of falls (IMPROveFALL) trial. Age and Ageing 2017;46(1):142-6. [DOI: 10.1093/ageing/afw161]

Cateau 2021 {published data only}

Cateau D, Ballabeni P, Niquille A. Effects of an interprofessional deprescribing intervention in Swiss nursing homes: the Individual Deprescribing Intervention (IDeI) randomised controlled trial. BMC Geriatrics 2021;21(1):655. [DOI: 10.1186/s12877-021-02465-7]

Cohen 2021 {published data only}

Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respiratory Medicine 2021;9(3):275-84. [DOI: 10.1016/S2213-2600(20)30558-0]

Crisafulli 2021 {published data only}

Crisafulli S, Luxi N, Coppini R, Capuano A, Scavone C, Zinzi A, et al. Anti-hypertensive drugs deprescribing: an updated systematic review of clinical trials. BMC Family Practice 2021;22(1):208. [DOI: 10.1186/s12875-021-01557-y]

CTRI/2021/01/030199 2021 {published data only}

CTRI/2021/01/030199. Continuation or stopping antihypertensives in patients undergoing non-cardiac surgery. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2021/01/030199 2021.

Curtin 2020 {published data only}

Curtin D, Jennings E, Daunt R, Curtin S, Randles M, Gallagher P, et al. Deprescribing in Older People Approaching End of Life: a Randomized Controlled Trial Using STOPPFrail Criteria. Journal of the American Geriatrics Society 2020;68(4):762-9. [DOI: 10.1111/jgs.16278]

Ekbom 1992 {published data only}

Ekbom TSA. Risks of Hypertension in the Elderly (Doctoral Dissertation). Lund: Lund University, 1992.

ENOS Trial Investigators 2015 {published data only}

* ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet 2015;385(9968):617-28. [DOI: 10.1016/S0140-6736(14)61121-1]
Krishnan K, Scutt P, Woodhouse L, Adami A, Becker JL, Cala LA, et al. Continuing versus stopping prestroke antihypertensive therapy in acute intracerebral hemorrhage: a subgroup analysis of the efficacy of Nitric Oxide in Stroke trial. Journal of Stroke and Cerebrovascular Diseases 2016;25(5):1017-26. [DOI: http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.01.010]
Woodhouse LJ, Appleton JP, Scutt P, Everton L, Wilkinson G, Caso V, et al. Effect of continuing versus stopping pre-stroke antihypertensive agents within 12 h on outcome after stroke: a subgroup analysis of the efficacy of nitric oxide in stroke (ENOS) trial. EClinicalMedicine 2022;44:101274. [DOI: 10.1016/j.eclinm.2022.101274]

Gulla 2018 {published data only}

Gulla C, Flo E, Kjome RL, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. Journal of Geriatric Cardiology 2018;15(4):275-83. [DOI: 10.11909/j.issn.1671-5411.2018.04.011]

Guthrie 2002 {published data only}

Guthrie R, Reeves RA. Omapatrilat provides long-term control of hypertension: a randomized trial of treatment withdrawal. Journal of Clinical Hypertension 2002;4(3):169-72. [DOI: 10.1111/j.1524-6175.2002.01400.x]

Hansen 1983 {published data only}

Hansen AG, Jensen H, Laugesen LP, Petersen A. Withdrawal of antihypertensive drugs in the elderly. Acta Medica Scandinavica 1983;676:178-85. [DOI: https://doi.org/10.1111/j.0954-6820.1983.tb19342.x]

He 2018 {published data only}

He WJ, Zhong C, Xu T, Wang D, Sun Y, Bu X, et al. Early antihypertensive treatment and clinical outcomes in acute ischemic stroke: subgroup analysis by baseline blood pressure. Journal of Hypertension 2018;36(6):1372-81. [DOI: 10.1097/HJH.0000000000001690]

Hung 2014 {published data only}

Hung W. Self-monitoring and self-titration of antihypertensive medications result in better systolic blood pressure control. Journal of Clinical Outcomes Management 2014;21(10):444-8.

Jondeau 2009 {published data only}

Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. European Heart Journal 2009;30(18):2186-92. [DOI: 10.1093/eurheartj/ehp323]

Juraschek 2022 {published data only}

* Juraschek SP, Cluett JL, Belanger MJ, Anderson TS, Ishak A, Sahni S, et al. Effects of antihypertensive deprescribing strategies on blood pressure, adverse events, and orthostatic symptoms in older adults: results from TONE. American Journal of Hypertension 2022;35(4):337-46. [DOI: 10.1093/ajh/hpab171]
Kostis JB, Espeland MA, Appel L, Johnson KC, Pierce J, Wofford JL, Trial of nonpharmacologic interventions in the elderly (TONE) Cooperative Research Group. Does withdrawal of antihypertensive medication increase the risk of cardiovascular events? American Journal of Cardiology 1998;82:1501-8. [DOI: 10.1016/s0002-9149(98)00694-8]
NCT00000535 . Trial of Nonpharmacologic Interventions in Elderly (TONE). https://clinicaltrials.gov/show/NCT00000535 1999.

Kraut 2022 {published data only}

* Kraut R, Sadowski C, Youngson E, Faulder D, Korownyk C, Bakal J, et al. Antihypertensive deprescribing in long-term care: a randomized controlled trial (OPTIMIZEBP). BMJ Evidence-Based Medicine. Conference: Preventing Overdiagnosis Conference 2022. Calgary, AB Canada 2022;27(Suppl 1):A26-27.
NCT05047731 . Antihypertensive Deprescribing in Long-term Care (OptimizeBP). https://clinicaltrials.gov/show/NCT05047731 2021.

Kua 2021 {published data only}

Kua CH, Yeo CY, Tan PC, Char CW, Tan CW, Mak V, et al. Association of deprescribing with reduction in mortality and hospitalization: a pragmatic stepped-wedge cluster-randomized controlled trial. Journal of the American Medical Directors Association 2021;22(1):82-89.e3. [DOI: 10.1016/j.jamda.2020.03.012]

Langford 1985 {published data only}

Langford HG, Blaufox MD, Oberman A, Hawkins CM, Curb JD, Cutter GR, et al. Dietary therapy slows the return of hypertension after stopping prolonged medication. JAMA 1985;253(5):657-64. [PMID: 3881608]

Lewin 2012 {published data only}

Lewin A, Lasseter KC, Dong F, Whalen JC. Nebivolol withdrawal results in blood pressure returning toward pretreatment levels, but without rebound symptoms: phase IV randomized trial. Journal of the American Society of Hypertension 2012;6:228-36. [DOI: http://dx.doi.org/10.1016/j.jash.2012.02.002]

Luymes 2018 {published data only}

Luymes CH, Poortvliet RK, Van Geloven N, De Waal MW, Drewes YM, Blom JW, et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster randomised non-inferiority trial. BMC Medicine 2018;16(1):5. [DOI: 10.1186/s12916-017-0988-0]

Manning 2015 {published data only}

Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: post hoc analysis of the controlling hypertension and hypotension immediately post-stroke and continue or stop post-stroke antihypertensives collaborative study trials. Stroke 2015;46:1518-24. [DOI: http://dx.doi.org/10.1161/STROKEAHA.115.009078]

McDonald 2022 {published data only}

McDonald EG, Wu PE, Rashidi B, Wilson MG, Bortolussi-Courval E, Atique A, et al. The MedSafer study-electronic decision support for deprescribing in hospitalized older adults: a cluster randomized clinical trial. JAMA Internal Medicine 2022;182(3):265-73. [DOI: 10.1001/jamainternmed.2021.7429]

Medical Research Council Working Party 1986 {published data only}

Medical Research Council Working Party on Mild Hypertension. Course of blood pressure in mild hypertensives after withdrawal of long term antihypertensive treatment. British Medical Journal (Clinical Research Ed) 1986;293(6553):988-92. [DOI: 10.1136/bmj.293.6553.988]

Morgan 1994 {published data only}

Morgan T, Hopper H, Anderson A, Carricks L, Jones E, Johns J, et al. Can drug therapy be stopped in elderly hypertensive patients? Cardiology in the Elderly 1994;2(2):119-25.

Morselli 2022 {published data only}

Morselli F, Khong TK. Short-term effect of deprescribing antihypertensives in older people. Drug and Therapeutics Bulletin 2022;60(8):118-9. [DOI: 10.1136/dtb.2022.000030]

NCT00219063 2005 {published data only}

NCT00219063. A clinical study to compare an aliskiren based hypertensive regimen with a ramipril based one followed by a randomized withdrawal. clinicaltrials.gov/ct2/show/NCT00219063 2005.

NCT00785512 2008 {published data only}

NCT00785512. A study on the long-term efficacy of nebivolol after withdrawal of therapy. clinicaltrials.gov/ct2/show/NCT00785512 2008.

NCT05307666 2022 {published data only}

NCT05307666. MinMed: do older adults do better with less medication. https://clinicaltrials.gov/show/NCT05307666 2022.

NCT05585268 2022 {published data only}

NCT05585268. Electronic decision support for deprescribing in patients on hemodialysis (MedSafer-HD). https://clinicaltrials.gov/show/NCT05585268 2022.

Nelson 2003 {published data only}

Nelson MR, Reid CM, Krum H, Ryan P, Wing LM, McNeil JJ, Management Committee, Second Australian National Blood Pressure Study. Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2). American Journal of Hypertension 2003;16:39-45. [DOI: 10.1016/s0895-7061(02)03143-6]

Neusy 1989 {published data only}

Neusy AJ, Lowenstein J. Blood pressure and blood pressure variability following withdrawal of propranolol and clonidine. Journal of Clinical Pharmacology 1989;29:18-24. [DOI: 10.1002/j.1552-4604.1989.tb03232.x]

NHF 1981 {published data only}

National Heart Foundation. Treatment of mild hypertension in the elderly. A study initiated and administered by the National Heart Foundation (NHF) of Australia. Medical Journal of Australia 1981;2:398-402. [PMID: 7033745]

Ohkuma 2022 {published data only}

Ohkuma T, Harris K, Cooper M, Grobbee DE, Hamet P, Harrap S, et al. Short-term changes in serum potassium and the risk of subsequent vascular events and mortality: results from a randomized controlled trial of ACE inhibitors. Clinical Journal of the American Society of Nephrology 2022;17(8):1139-49. [DOI: 10.2215/CJN.00180122]

Pazan 2018 {published data only}

* Farhad P, Heinrich B, Helmut F, Christel W, Christina T, Alexandra KT, et al. Changes in prescription patterns in older hospitalized patients: the impact of FORTA on disease-related over- and under-treatments. European Journal of Clinical Pharmacology 2018;74(3):339-47. [DOI: 10.1007/s00228-017-2383-3]

Wehling M, Burkhardt H, Frohnhofen H, Weiss C, Throm C, Kuhn-Thiel A, et al. FORTAMET study: the impact of FORTA on disease-related over-and under-treatment in older hospitalized patients. European Geriatric Medicine. Conference: 14th International Congress of the European Geriatric Medicine Society, EuGMS 2018. Germany 2018;9(Suppl 1):S47.

Ponten 1982 {published data only}

Ponten J, Biber B, Henriksson BA, Hjalmarson A, Jonsteg C, Lundberg D. beta-Receptor blockade and neurolept anaesthesia. Withdrawal vs continuation of long-term therapy in gall-bladder and carotid artery surgery. Acta Anaesthesiologica Scandinavica 1982;26:576-88. [DOI: https://doi.org/10.1111/j.1399-6576.1982.tb01819.x]

Popa 1995 {published data only}

Popa G, Voiculescu V, Popa C, Stanescu A, Nistorescu A, Jipescu I. Stroke and hypertension. Antihypertensive therapy withdrawal. Romanian Journal of Neurology & Psychiatry 1995;33:29-35.

Potter 2016 {published data only}

ACTRN12611000370909. Deprescribing in frail older people: a randomised controlled trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12611000370909 2011.

* Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in frail older people: a randomised controlled trial. PloS One 2016;11(3):e0149984. [DOI: 10.1371/journal.pone.0149984]

Ramirez-Jimenez 2018 {published data only}

Ramirez-Jimenez M, Morales-Palomo F, Ortega JF, Mora-Rodriguez R. Effects of intense aerobic exercise and/or antihypertensive medication in individuals with metabolic syndrome. Scandinavian Journal of Medicine & Science in Sports 2018;28(9):2042-51. [DOI: 10.1111/sms.13218]

Ramirez-Jimenez 2021 {published data only}

Ramirez Jimenez M, Morales-Palomo F, Moreno-Cabanas A, Alvarez-Jimenez L, Ortega JF, Mora-Rodriguez R. Additive blood-pressure lowering effect of aerobic training on antihypertensive medication in metabolic syndrome individuals. Conference: European Meeting on Hypertension and Cardiovascular Protection and International Society of Hypertension, ESH-ISH 2021. Virtual 2021;39(Suppl 1):e393.

* Ramirez-Jimenez M, Morales-Palomo F, Moreno-Cabanas A, Alvarez-Jimenez L, Ortega JF, Mora-Rodriguez R. Effects of antihypertensive medication and high-intensity interval training in hypertensive metabolic syndrome individuals. Scandinavian Journal of Medicine & Science in Sports 2021;31(7):1411-9. [DOI: 10.1111/sms.13949]

Robinson 2010 {published data only}

COSSACS Trial Group. COSSACS (Continue or Stop post-Stroke Antihypertensives Collaborative Study): rationale and design. Journal of Hypertension 2005;23(2):455-8. [DOI: http://dx.doi.org/10.1097/00004872-200502000-00029]

Eames PJ, Potter JF, Robinson TG. Continue or stop post-stroke antihypertensives collaborative study (COSSACS). In: International Stroke Conference. 2005.

Ferrari J. Effects of antihypertensive treatment after acute stroke in the Continue or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Journal fur Neurologie, Neurochirurgie und Psychiatrie 2010;11:85-6.

* Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, et al: COSSACS Investigators. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurology 2010;9:767-75. [DOI: http://dx.doi.org/10.1016/S1474-4422(10)70163-0]
Robinson TG, Potter JF. The continue or stop post-stroke antihypertensives collaborative study (COSSACS). Cerebrovascular Diseases 2003;16:Suppl 4.
Robinson TG, Potter JF, COSSACS Group. The continue or stop post-stroke antihypertensives collaborative study (COSSACS). Age and Ageing 2003;32(Suppl 1):40.

Ruoff 1986 {published data only}

Ruoff G. Effect of withdrawal of terazosin therapy in patients with hypertension. American Journal of Medicine 1986;80:35-41.

Sharma 2022 {published data only}

Sharma A, Elharram M, Afilalo J, Flannery A, Afilalo M, Tselios C, et al. A randomized controlled trial of renin-angiotensin-aldosterone system inhibitor management in patients admitted in hospital with COVID-19. American Heart Journal 2022;247:76-89. [DOI: 10.1016/j.ahj.2022.01.015]

Sheppard 2020 {published data only}

Burt J, Sheppard J, Lown M, Mant J, Little P, McManus RJ. OPtimising Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE): a protocol for a randomised controlled trial. Pharmacoepidemiology and Drug Safety 2017;26(Suppl 1):6-7. [DOI: 10.1136/bmjopen-2018-022930]
Jowett S, Kodabuckus S, Ford GA, Hobbs FD, Lown M, Mant J, et al. Cost-effectiveness of antihypertensive deprescribing in primary care: a markov modelling study using data from the optimise trial. Hypertension 2022;79(5):1122-31. [DOI: 10.1161/HYPERTENSIONAHA]
Sheppard J, Burt J, Lown M, Temple E, Lowe R, Fraser R, et al. Short-term safety of antihypertensive medication reduction in multi-morbid patients with mild hypertension: the optimise randomised controlled non-inferiority trial. Journal of Hypertension 2021;39(Suppl 1):e369-70.
Sheppard J, Lown M, Burt J, Temple E, Ford G, Hobbs R, et al. Optimal drugs for medication reduction: secondary analysis of the optimise medication reduction trial. Journal of Hypertension. Conference: European Meeting on Hypertension and Cardiovascular Protection and International Society of Hypertension, ESH-ISH 2021. Virtual 2021;39(Suppl 1):e52.
* Sheppard JP, Burt J, Lown M, Temple E, Lowe R, Fraser R, et al. Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older: the OPTIMISE randomized clinical trial. JAMA 2020;323(20):2039-51. [DOI: 10.1001/jama.2020.4871]
Sheppard JP, Lown M, Burt J, Ford GA, Hobbs FDR, Little P, et al. Blood pressure changes following antihypertensive medication reduction, by drug class and dose chosen for withdrawal: exploratory analysis of data from the OPTIMISE trial. Frontiers in Pharmacology 2021;12:619088. [DOI: 10.3389/fphar.2021.619088]

Stange 2013 {published data only}

Stange D, Kriston L, von-Wolff A, Baehr M, Dartsch DC. Reducing cardiovascular medication complexity in a German university hospital: effects of a structured pharmaceutical management intervention on adherence. Journal of Managed Care Pharmacy 2013;19(5):396-407. [DOI: 10.18553/jmcp.2013.19.5.396]

Szam 1981 {published data only}

Szam I, Hollo J. Antihypertensive effect of guanfacine: long-term 'once-a-day' treatment and sudden withdrawal. Clinical Science 1981;61(Suppl 7):469s-71s. [DOI: 10.1042/cs061469s]

Vaur 1998 {published data only}

Vaur L, Bobrie G, Dutrey-Dupagne C, Dubroca I, Vaisse B, D'Yvoire MB, et al. Short-term effects of withdrawing angiotensin converting enzyme inhibitor therapy on home self-measured blood pressure in hypertensive patients. American Journal of Hypertension 1998;11:165-73. [DOI: 10.1016/s0895-7061(97)00420-2]

Veterans Administration Cooperative 1975 {published data only}

Veterans Administration Cooperative Study Group on Antihypertensive Agents. Return of elevated blood pressure after withdrawal of antihypertensive drugs. Circulation 1975;51:1107-13. [DOI: 10.1161/01.cir.51.6.1107]

Wachtell 2022 {published data only}

Wachtell K, Julius S, Okin PM, Greve AM, Devereux RB, Oparil S, et al. Cardiovascular outcomes in hypertensive patients who discontinue study medication in a large outcome trial. The life study. Hypertension 2022;79:AP221. [DOI: https://doi.org/10.1161/hyp.79.suppl_1.P221]

Xu 2017 {published data only}

* Xu T, Zhang Y, Bu X, Wang D, Sun Y, Chen CS, et al, CATIS Investigators. Blood pressure reduction in acute ischemic stroke according to time to treatment: a subgroup analysis of the China Antihypertensive Trial in Acute Ischemic Stroke trial. Journal of Hypertension 2017;35(6):1244-51. [DOI: 10.1097/HJH.0000000000001288]

Zhang R, Zhong C, Zhang Y, Xie X, Zhu Z, Wang A, et al. Immediate antihypertensive treatment for patients with acute ischemic stroke with or without history of hypertension: a secondary analysis of the CATIS randomized clinical trial. JAMA Network Open 2019;2(7):e198103. [DOI: 10.1001/jamanetworkopen.2019.8103]

Yang 2021 {published data only}

Yang YF, Zhu YJ, Long YQ, Liu HY, Shan XS, Feng XM, et al. Withholding vs. continuing angiotensin-converting enzyme inhibitors or angiotensin receptor blockers before non-cardiac surgery in older patients: study protocol for a multicenter randomized controlled trial. Frontiers in Medicine 2021;8:654700. [DOI: 10.3389/fmed.2021.654700]

Zhang 2019 {published data only}

Zhang Y, Liang M, Sun C, Qu G, Shi T, Min M, et al. Effect of intensive lowering of systolic blood pressure treatment on heart failure events: a meta-analysis of randomized controlled studies. Journal of Human Hypertension 2019;33(9):648-57. [DOI: 10.1038/s41371-019-0221-z]

Additional references

Albasri 2021

Albasri A, Hattle M, Koshiaris C, Dunnigan A, Paxton B, Fox SE, et al. Association between antihypertensive treatment and adverse events: systematic review and meta-analysis. British Medical Journal 2021;372:n189. [DOI: 10.1136/bmj.n189]

Bogaerts 2022

Bogaerts JM, von Ballmoos LM, Achterberg WP, Gussekloo J, Streit S, van der Ploeg MA, et al. Do we AGREE on the targets of antihypertensive drug treatment in older adults: a systematic review of guidelines on primary prevention of cardiovascular diseases. Age and Ageing 2022;51(1):afab192. [DOI: 10.1093/ageing/afab192]

Chatzis 2023

Chatzis DG, Magounaki K, Pantazopoulos I, Beltsios ET, Katsi V, Tsioufis KP. Current management of hypertension in older adults. Drugs & Aging 2023;40(5):407-16. [DOI: 10.1007/s40266-023-01013-9]

Crisafulli 2021

Crisafulli S, Luxi N, Coppini R, Capuano A, Scavone C, Zinzi A, et al. Anti-hypertensive drugs deprescribing: an updated systematic review of clinical trials. BMC Family Practice 2021;22:1-11. [DOI: 10.1186/s12875-021-01557-y]

Dunlay 2016

Dunlay SM, Chamberlain AM . Multimorbidity in older patients with cardiovascular disease. Current Cardiovascular Risk Reports 2016;10:1-9. [DOI: 10.1007/s12170-016-0491-8]

Ekbom 1994

Ekbom T, Lindholm LH, Odén A, Dahlöf B, Hansson L, Wester PO, et al. A 5-year prospective, observational study of the withdrawal of antihypertensive treatment in elderly people. Journal of Internal Medicine 1994;235(6):581-8. [DOI: 10.1111/j.1365-2796.1994.tb01265.x]

Froom 1997

Froom J, Trilling JS, Yeh SS, Gomolin IH, Filkin AM, Grimson RC. Withdrawal of antihypertensive medications. Journal of the American Board of Family Practice 1997;10(4):249-58. [PMID: 9228619]

Fryar 2017

Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015-2016. https://www.cdc.gov/nchs/products/databriefs/db289.htm (accessed prior to 28 May 2020).

Gnjidic 2021

Gnjidic D, Reeve E. Deprescribing: what do we know, and where to next? British Journal of Clinical Pharmacology 2021;87(3):722-4. [DOI: 10.1111/bcp.14525]

Gnjidic 2022

Gnjidic D, Johansson M, Meng DM, Farrell B, Langford A, Reeve E. Achieving sustainable healthcare through deprescribing. Cochrane Database of Systematic Reviews 2022;10:ED000159. [DOI: 10.1002/14651858.ED000159]

Goshgarian 2019

Goshgarian C, Gorelick PB. Perspectives on the relation of blood pressure and cognition in the elderly. Trends in Cardiovascular Medicine 2019;29(1):12-8. [DOI: 10.1016/j.tcm.2018.05.011]

Higgins 2017

Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0;(updated June 2017), Cochrane, 2017:Available from www.training.cochrane.org/handbook.

Ikeda 2014

Ikeda N, Sapienza D, Guerrero R, Aekplakorn W, Naghavi M, Mokdad AH, et al. Control of hypertension with medication: a comparative analysis of national surveys in 20 countries. Bulletin of the World Health Organization 2014;92(1):10-9C. [DOI: 10.2471/BLT.13.121954]

Iyer 2008

Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older. Drugs & Aging 2008;25(12):1021-31. [DOI: 10.2165/0002512-200825120-00004]

Johansson 2019

Johansson M, Bero L, Bonfill X, Bruschettini M, Garner S, Glenton C, et al. Cochrane sustainable healthcare: evidence for action on too much medicine. Cochrane Database of Systematic Reviews 2019;12:ED000143. [DOI: 10.1002/14651858.ED000143]

Jongstra 2016

Jongstra S, Harrison JK, Quinn TJ, Richard E. Antihypertensive withdrawal for the prevention of cognitive decline. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No: CD011971. [DOI: 10.1002/14651858.CD011971.pub2]

Lee 2022

Lee GB, Etherton-Beer C, Hosking SM, Pasco JA, Page AT. The patterns and implications of potentially suboptimal medicine regimens among older adults: a narrative review. Therapeutic Advances in Drug Safety 2022;13:20420986221100117. [DOI: 10.1177/20420986221100117]

Mancia 2023

Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). Journal of Hypertension 2023;41(12):1874-2071. [DOI: 10.1097/HJH.0000000000003480]

Mensah 2017

Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in cardiovascular mortality: possible causes and implications. Circulation Research 2017;120(2):366-80. [DOI: 10.1161/CIRCRESAHA.116.309115]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009;151(4):264-9. [DOI: 10.7326/0003-4819-151-4-200908180-00135]

Morel 2022

Morel T, Nguyen-Soenen J, Thompson W, Fournier JP. Development and validation of search filters to identify articles on deprescribing in Medline and Embase. BMC Medical Research Methodology 2022;22(1):1-9.

[DOI: 10.1186/s12874-022-01515-x]

Moriarty 2022

Moriarty F, Thompson W, Boland F. Methods for evaluating the benefit and harms of deprescribing in observational research using routinely collected data. Research in Social and Administrative Pharmacy 2022;18:2269-75. [DOI: 10.1016/j.sapharm.2021.05.007]

Musini 2019

Musini VM, Tejani AM, Bassett K, Puil L, Wright JM. Pharmacotherapy for hypertension in adults 60 years or older. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No: CD000028. [DOI: 10.1002/14651858.CD000028.pub3]

National Heart Foundation of Australia 2016

National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. www.heartfoundation.org.au/getmedia/c83511ab-835a-4fcf-96f5-88d770582ddc/PRO-167_Hypertension-guideline-2016_WEB.pdfMelbourne (accessed prior to 28 May 2020). [ISBN: 978-174345-110-6]

Nelson 2001

Nelson M, Reid C, Krum H, McNeil J. A systematic review of predictors of maintenance of normotension after withdrawal of antihypertensive drugs. American Journal of Hypertension 2001;14(2):98-105. [DOI: 10.1016/s0895-7061(00)01246-2]

NICE 2016

NICE: National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. https://www.nice.org.uk/guidance/ng56/resources/multimorbidity-clinical-assessment-and-management-pdf-1837516654789 2016:ng56.

NICE 2019

NICE: National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management.. www.nice.org.uk/guidance/ng136 2019:ng136.

NICE 2022

NICE: National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213 2022:ng136.

Oktora 2019

Oktora MP, Denig P, Bos JH, Schuiling-Veninga CC, Hak E. Trends in polypharmacy and dispensed drugs among adults in the Netherlands as compared to the United States. PLOS One 2019;14(3):e0214240. [DOI: 10.1371/journal.pone.0214240]

Page 2016

Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. British Journal of Clinical Pharmacology 2016;82(3):583-623. [DOI: doi: 10.1111/bcp.12975]

Page 2019

Page AT, Falster MO, Litchfield M, Pearson SA, Etherton-Beer C. Polypharmacy among older Australians, 2006–2017: a population-based study. Medical Journal of Australia 2019;211(2):71-5. [DOI: 10.5694/mja2.50244]

Parekh 2017

Parekh N, Page A, Ali K, Davies K, Rajkumar C. A practical approach to the pharmacological management of hypertension in older people. Therapeutic Advances in Drug Safety 2017;8(4):117-32. [DOI: 10.1177/2042098616682721]

Publish or Perish 2022 [Computer program]

Publish or Perish. Version 8.8. Harzing AW, 2022. Available at https://harzing.com/resources/publish-or-perish.

Reeve 2014

Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. The benefits and harms of deprescribing. Medical Journal of Australia 2014;201:386-9. [DOI: 10.5694/mja13.00200]

Reeve 2014b

Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence based, patient-centred deprescribing process. British Journal of Clinical Pharmacology 2014;78(4):738-47. [DOI: doi: 10.1111/bcp.12386]

Reeve 2015

Reeve E, Wiese M, Mangoni A. Alterations in drug disposition in older adults. Expert Opinion On Drug Metabolism and Toxicology 2015;11(4):491-508. [DOI: 10.1517/17425255.2015.1004310]

Reeve 2017

Reeve E, Thompson W, Farrell B. Deprescribing: a narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. European Journal of Internal Medicine 2017;38:3-11. [DOI: 10.1016/j.ejim.2016.12.021]

RevMan Web 2024 [Computer program]

RevMan Web 2024. Copenhagen: Nordic Cochrane Centre, the Cochrane Collaboration, 2024.

Sawan 2021

Sawan MJ, Moga DC, Ma MJ, Ng JC, Johnell K, Gnjidic D. The value of deprescribing in older adults with dementia: a narrative review. Expert Review of Clinical Pharmacology 2021;14(11):1367-82. [DOI: 10.1080/17512433.2021.1961576]

Sawan 2022

Sawan MJ, Jeon YH, Hilmer SN, Chen TF. Perspectives of residents on shared decision making in medication management: a qualitative study. International Psychogeriatrics 2022;34(10):929-39. [DOI: 10.1017/S1041610222000205]

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH (editors). Chapter 11: presenting results and 'summary of findings' tables. In: Higgins JPT, Green S, editor(s). Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Scott 2015

Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Internal Medicine 2015;175:827-34. [DOI: 10.1001/jamainternmed.2015.0324]

Scott 2019

Scott IA, Hilmer SN, Le Couteur DG. Going beyond the guidelines in individualising the use of antihypertensive drugs in older patients. Drugs and Aging 2019;36(8):675-85. [DOI: 10.1007/s40266-019-00683-8]

Shenkin 2017

Shenkin SD, Harrison JK, Wilkinson T, Dodds RM, Ioannidis JP. Systematic reviews: guidance relevant for studies of older people. Age & Ageing 2017;46(5):722-8. [DOI: 10.1093/ageing/afx185]

Sheppard 2022

Sheppard JP, Benetos A, McManus RJ. Antihypertensive deprescribing in older adults: a practical guide. Current Hypertension Reports 2022;24:571–80. [DOI: 10.1007/s11906-022-01215-3]

Sheppard 2023

Sheppard JP, Koshiaris C, Stevens R, Lay-Flurrie S, Banerjee A, Bellows BK, et al. The association between antihypertensive treatment and serious adverse events by age and frailty: a cohort study. PLOS Medicine 2023;20(4):e1004223. [DOI: 10.1371/journal.pmed.1004223]

Steinman 2006

Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. Journal of the American Geriatrics Society 2006;54(10):1516-23. [DOI: 10.1111/j.1532-5415.2006.00889.x]

Sterne 2014

Sterne JA, Higgins JP, Reeves BC, the development group for ACROBAT-NRSI. A Cochrane risk of bias assessment tool: for non-randomised studies of interventions (ACROBAT-NRSI). Available from www.riskofbias.info (accessed prior to 28 May 2020);(1.0.0).

Unger 2020

Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 international society of hypertension global hypertension practice guidelines. Hypertension 2020;75:1334–57. [DOI: 10.1161/HYPERTENSIONAHA]

Van Der Velde 2007

Van Der Velde N, Stricker BH, Pols HA, Van Der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. British Journal of Clinical Pharmacology 2007;63(2):232-7. [DOI: 10.1111/j.1365-2125.2006.02736.x]

Van der Wardt 2017

Van der Wardt V, Harrison JK, Welsh T, Conroy S, Gladman J. Withdrawal of antihypertensive medication: a systematic review. Journal of Hypertension 2017;35(9):1742. [DOI: 10.1097/HJH.0000000000001405]

Wastesson 2018

Wastesson JW, Morin L, Tan EC, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opinion on Drug Safety 2018;17(12):1185-96. [DOI: 10.1080/14740338.2018.1546841]

Weir 2022

Weir KR, Ailabouni NJ, Schneider CR, Hilmer SN, Reeve E. Consumer attitudes towards deprescribing: a systematic review and meta-analysis. The Journals of Gerontology: Series A (Medical Sciences) 2022;77(5):1020-34. [DOI: 10.1093/gerona/glab222]

Whelton 2018

Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb DC, et al, American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS /APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2018;71:2199-269. [DOI: 10.1161/HYP.0000000000000080]

Williams 2018

Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al, Task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). European Heart Journal 2018;33(1):3021-104. [DOI: 10.1093/eurheartj/ehy339]

Woolcott 2009

Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Archives of Internal Medicine 2009;169(21):1952-60. [DOI: 10.1001/archinternmed.2009.357]

References to other published versions of this review

Babar 2017

Babar ZU, Gammie TM, Gnjidic D, Reeve E, Jordan-Cole V, Hilmer SN, et al. Withdrawal of antihypertensive drugs in older people. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No: CD012572. [DOI: 10.1002/14651858.CD012572]

Reeve 2020

Reeve E, Jordan V, Thompson W, Sawan M, Todd A, Gammie TM, et al. Withdrawal of antihypertensive drugs in older people. Cochrane Database of Systematic Reviews June 2020, Issue CD012572. Art. No: CD012572. [DOI: 10.1002/14651858.CD012572.pub2]

Additional tables

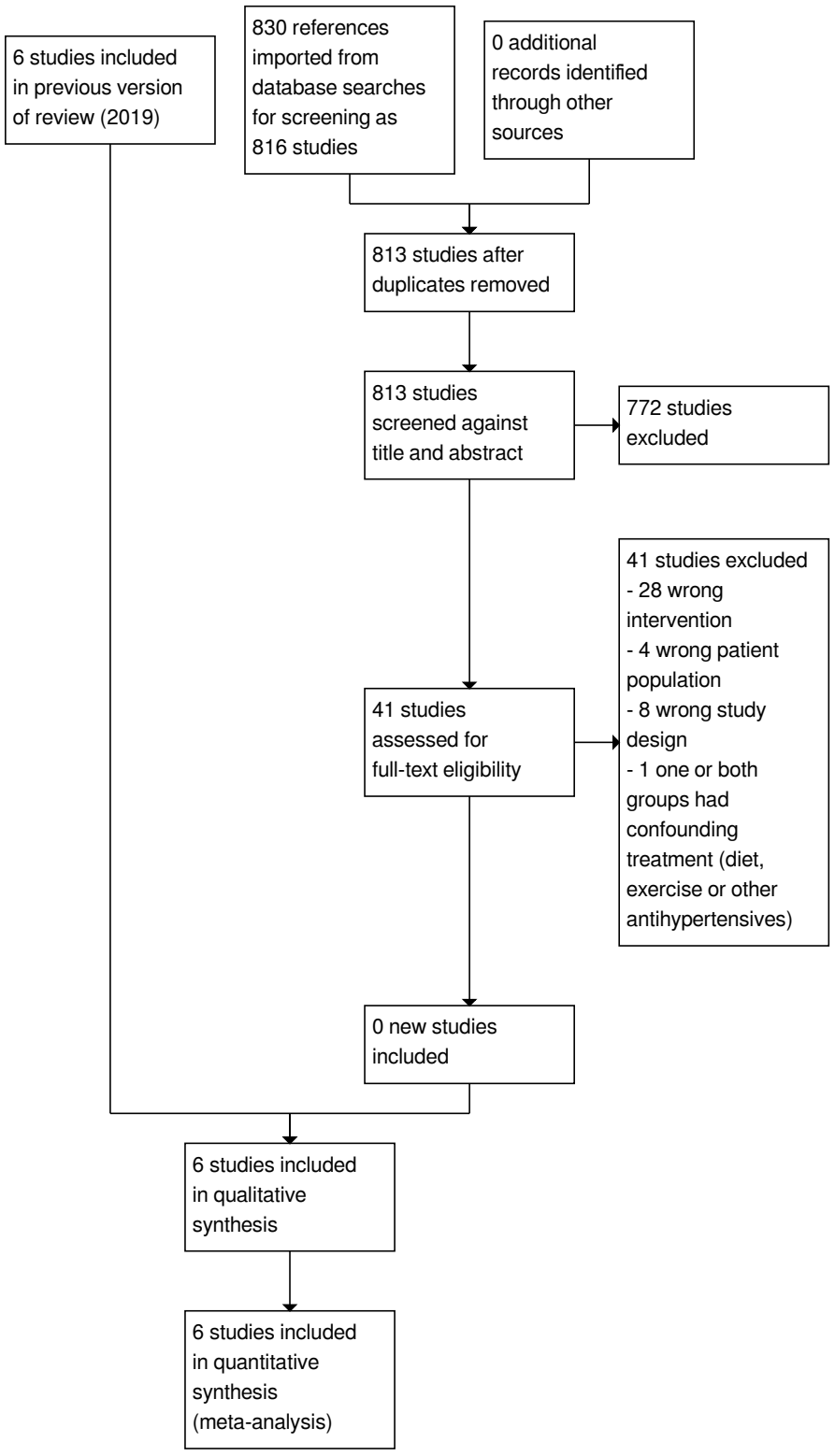
Table 1

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 furosemide 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.

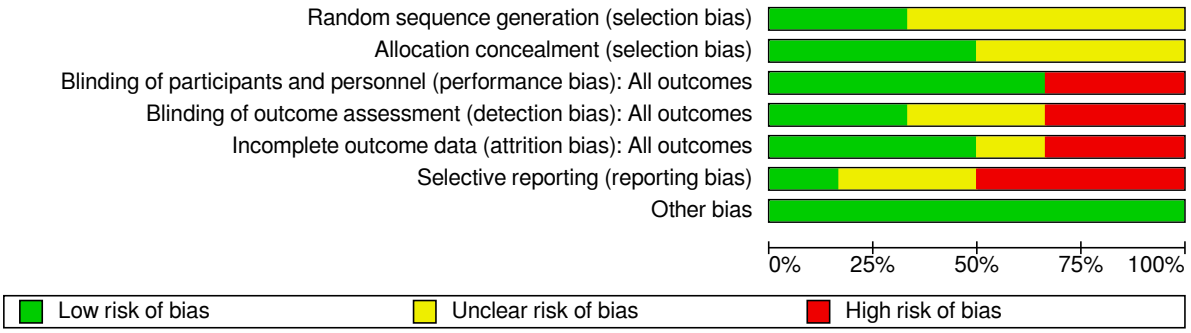
BP: Blood pressure
SBP: Systolic blood pressure

Figure 1



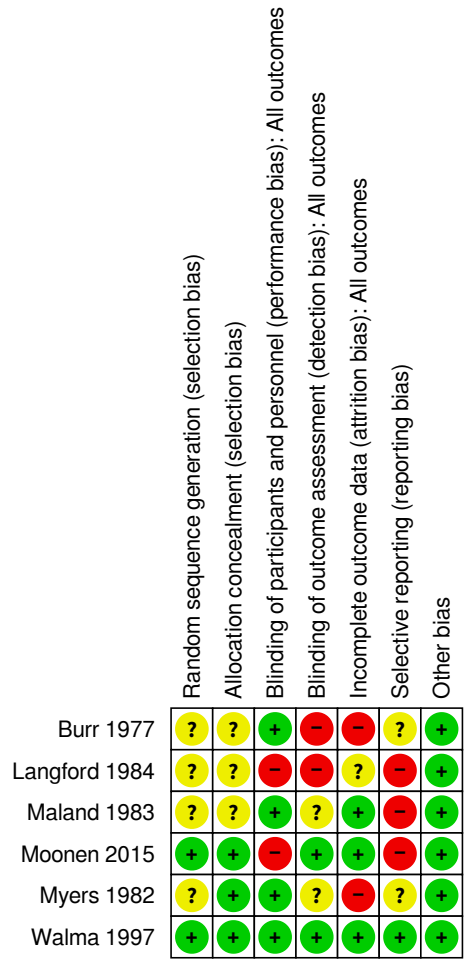
Study flow diagram.

Figure 2



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

Figure 3

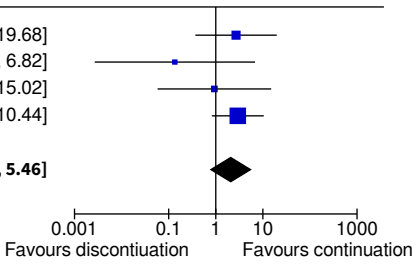


Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Analysis 1.1

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

Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable
Heterogeneity: $Chi^2 = 2.53$, df = 3 (P = 0.47); $I^2 = 0\%$



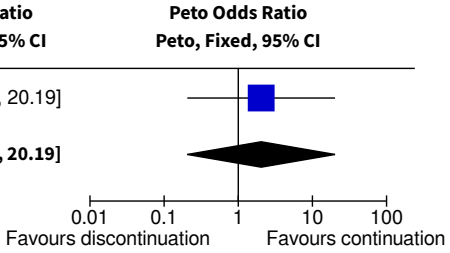
Footnotes
[a]12 weeks follow-up
[b]12 months follow-up
[c]16 weeks follow-up
[d]12 month follow-up

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

Analysis 1.2

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

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

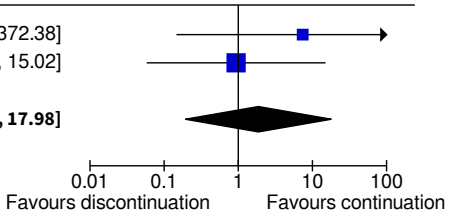


Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 2: Cardiovascular mortality

Analysis 1.3

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

Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable
Heterogeneity: $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0\%$



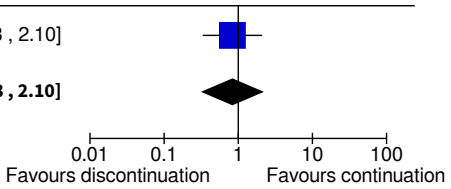
Footnotes
[a]Follow up at 12-months
[b]Follow-up at 16 weeks

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

Analysis 1.4

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

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



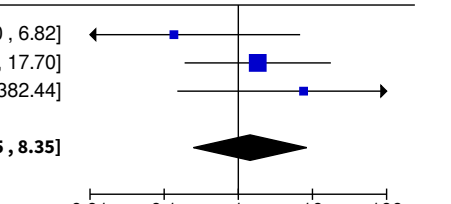
Footnotes
[a]16 weeks follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 4: Hospitalisation

Analysis 1.5

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

Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable
Heterogeneity: $Chi^2 = 2.13$, df = 2 (P = 0.34); $I^2 = 6\%$



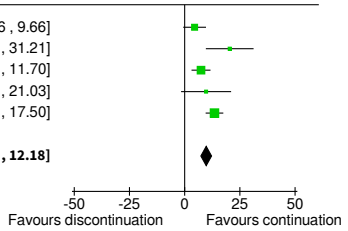
Footnotes
[a]12 months follow-up
[b]16 weeks follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 5: Stroke (fatal + nonfatal + TIA)

Analysis 1.6

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

Test for overall effect: Z = 7.89 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: $Chi^2 = 12.23$, df = 4 (P = 0.02); $I^2 = 67\%$



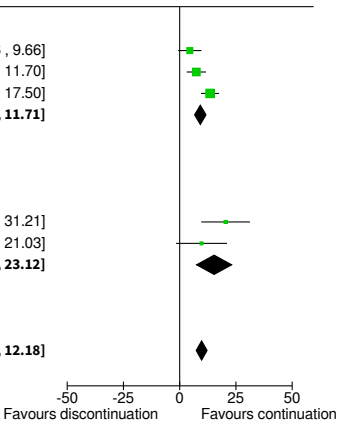
Footnotes
[a]5-12 weeks follow-up
[b]12 months follow-up, SD imputed
[c]16 weeks follow-up
[d]12 months follow-up
[e]6 months follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 6: Systolic blood pressure

Analysis 1.7

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Less than 12 months								
Burr 1977[a]	136.3	12.7	41	131.8	12	48	22.0%	4.50 [-0.66 , 9.66]
Moonen 2015[b]	5.4	21.46625258	180	-2	19.8997487421324	176	31.7%	7.40 [3.10 , 11.70]
Walma 1997[c]	8.8	17.31	102	-4.7	11.0875	100	36.6%	13.50 [9.50 , 17.50]
Subtotal			**323**			**324**	**90.4%**	**9.17 [6.62 , 11.71]**
Test for overall effect: Z = 7.05 (P < 0.00001)								
Heterogeneity: Chi² = 8.30, df = 2 (P = 0.02); I² = 76%								
1.7.2 12 months or longer								
Maland 1983[d]	143.2	23.45548976252679	31	122.8	19.79898987322333	31	5.0%	20.40 [9.59 , 31.21]
Myers 1982[e]	135	23.45548976252679	26	125.3	19.79898987322333	32	4.6%	9.70 [-1.63 , 21.03]
Subtotal			**57**			**63**	**9.6%**	**15.30 [7.48 , 23.12]**
Test for overall effect: Z = 3.84 (P = 0.0001)								
Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%								
Total			**380**			**387**	**100.0%**	**9.75 [7.33 , 12.18]**

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%
Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%



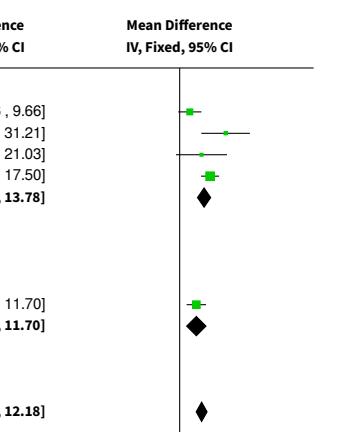
Footnotes
[a]5-12 weeks follow-up
[b]16 weeks follow-up
[c]6 months follow-up
[d]12 months follow-up, SD imputed
[e]12 months follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 7: Systolic blood pressure subgrouped on duration

Analysis 1.8

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

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%
Heterogeneity: Chi² = 12.23, df = 4 (P = 0.02); I² = 67%



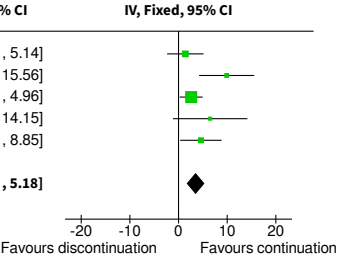
Footnotes
[a]5-12 weeks follow-up
[b]12 months follow-up, SD imputed
[c]12 months follow-up
[d]6 months follow-up
[e]16 weeks follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 8: Systolic blood pressure subgrouped on drug type

Analysis 1.9

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

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

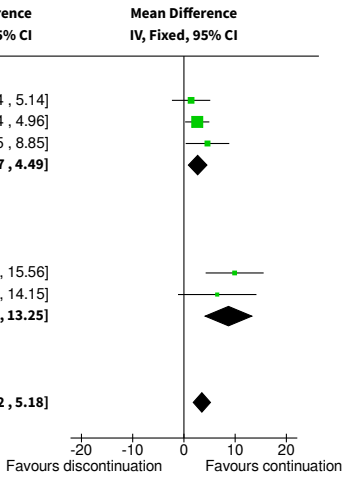


Footnotes
[a]5-12 weeks follow-up
[b]12 months follow-up, SD imputed
[c]16 weeks follow-up
[d]12 months follow-up
[e]6 months follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 9: Diastolic blood pressure

Analysis 1.10

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Less than 12 months								
Burr 1977[a]	82.4	8.3	41	81	9.6	47	20.2%	1.40 [-2.34 , 5.14]
Moonen 2015[b]	1.3	12.07476707849883	180	-1.3	10.61319932913728	176	50.6%	2.60 [0.24 , 4.96]
Walma 1997[c]	4.8	11.2006	102	0.2	18.6472	100	15.6%	4.60 [0.35 , 8.85]
Subtotal			**323**			**323**	**86.4%**	**2.68 [0.87 , 4.49]**
Test for overall effect: Z = 2.91 (P = 0.004)								
Heterogeneity: Chi^2 = 1.24, df = 2 (P = 0.54); I^2 = 0%								
1.10.2 12 months or longer								
Maland 1983[d]	7.3	12.07476707849883	31	-2.6	10.61319932913728	31	8.8%	9.90 [4.24 , 15.56]
Myers 1982[e]	76	15.8745	28	69.5	14.1421	32	4.8%	6.50 [-1.15 , 14.15]
Subtotal			**59**			**63**	**13.6%**	**8.70 [4.15 , 13.25]**
Test for overall effect: Z = 3.75 (P = 0.0002)								
Heterogeneity: Chi^2 = 0.49, df = 1 (P = 0.48); I^2 = 0%								
Total			**382**			**386**	**100.0%**	**3.50 [1.82 , 5.18]**
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi^2 = 5.80, df = 1 (P = 0.02), I^2 = 82.8%								
Heterogeneity: Chi^2 = 7.53, df = 4 (P = 0.11); I^2 = 47%								



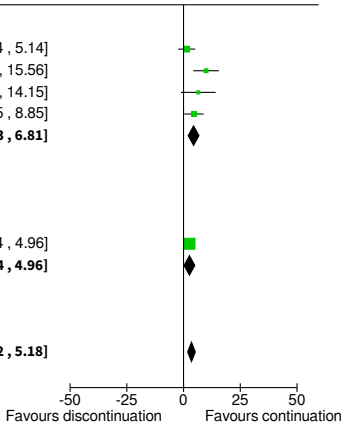
Footnotes

[a]5-12 weeks follow-up
[b]16 weeks follow-up
[c]6 months follow-up
[d]12 months follow-up, SD imputed
[e]12 months follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 10: Diastolic blood pressure subgrouped on duration

Analysis 1.11

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



Footnotes

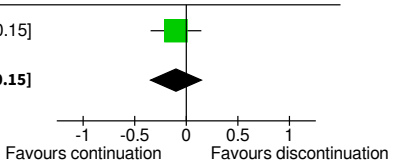
[a]5-12 weeks follow-up
[b]12 months follow-up, SD imputed
[c]12 months follow-up
[d]6 months follow-up
[e]16 weeks follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 11: Diastolic blood pressure subgrouped on drug type

Analysis 1.12

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

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



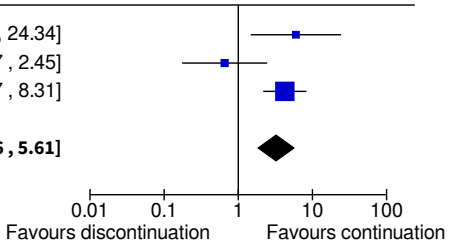
Footnotes
[a]16 weeks follow-up

Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 12: Quality of life

Analysis 1.13

Study or Subgroup	Discontinuation Events	Total	Continuation Events	Total	Weight	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		**171**		**170**	**100.0%**	**3.23 [1.86 , 5.61]**
Total events:	46		16			

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



Comparison 1: Discontinuation by no treatment/placebo of antihypertensives vs Continuation, Outcome 13: Sucess rate - withdrawal/resumption due to hypertension or other clinical reason