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Blood pressure targets for hypertension in older adults (Review)

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[Intervention Review]

Blood pressure targets for hypertension in older adults

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ABSTRACT

Background

Eight out of 10 major antihypertensive trials in older adults attempted to achieve a target systolic blood pressure (BP) less than 160 mmHg. Collectively these trials demonstrated benefit for treatment, as compared to no treatment, for an older adult with BP greater than 160 mmHg. However an even lower BP target of less than 140 mmHg is commonly applied to all age groups. At the present time it is not known whether a lower or higher BP target is associated with better cardiovascular outcomes in older adults.

Objectives

To assess the effects of a higher (less than 150 to 160/95 to 105 mmHg) BP target compared to the lower BP target of less than 140/90 mmHg in hypertensive adults 65 years of age or older.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials up to February 2017: the Cochrane Hypertension Specialised Register, MEDLINE, Embase, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. We also contacted authors of relevant papers regarding further published and unpublished work.

Selection criteria

Randomised trials, of at least one year's duration, conducted on hypertensive adults aged 65 years or older, which report the effect on mortality and morbidity of a higher systolic or diastolic BP treatment target (whether ambulatory, home, or office measurements) in the range of systolic BP less than 150 to 160 mmHg or diastolic BP less than 95 to 105 mmHg as compared to a lower BP treatment target of less than 140/90 mmHg or lower.

Data collection and analysis

Two authors independently screened and selected trials for inclusion, assessed risk of bias, and extracted data. We combined data for dichotomous outcomes using the risk ratio (RR) with 95% confidence interval (CI) and for continuous outcomes we used mean difference (MD). Primary outcomes were all-cause mortality, stroke, institutionalisation, and cardiovascular serious adverse events. Secondary outcomes included cardiovascular mortality, non-cardiovascular mortality, unplanned hospitalisation, each component of cardiovascular serious adverse events separately (including cerebrovascular disease, cardiac disease, vascular disease, and renal failure), total serious adverse events, total minor adverse events, withdrawals due to adverse effects, systolic BP achieved, and diastolic BP achieved.

Main results

We found and included three unblinded randomised trials in 8221 older adults (mean age 74.8 years), in which higher BP targets of less than 150/90 mmHg (two trials) and less than 160/90 mmHg (one trial) were compared to a lower target of less than 140/90 mmHg. Treatment to the two different BP targets over two to four years failed to produce a difference in any of our primary outcomes, including all-cause mortality (RR 1.24 95% CI 0.99 to 1.54), stroke (RR 1.25 95% CI 0.94 to 1.67) and total cardiovascular serious adverse events (RR 1.19 95% CI 0.98 to 1.45). However, the 95% confidence intervals of these outcomes suggest the lower BP target is probably not worse, and might offer a clinically important benefit. We judged all comparisons to be based on low-quality evidence. Data on adverse effects were not available from all trials and not different, including total serious adverse events, total minor adverse events, and withdrawals due to adverse effects.

Authors' conclusions

At the present time there is insufficient evidence to know whether a higher BP target (less than150 to 160/95 to 105 mmHg) or a lower BP target (less than 140/90 mmHg) is better for older adults with high BP. Additional good-quality trials assessing BP targets in this population are needed.

PLAIN LANGUAGE SUMMARY

Blood pressure targets for hypertension in older adults

Review question

What is the optimal blood pressure (BP) target when treating older adults with high blood pressure?

Background

Elevated BP in older adults is common and higher pressures increase the risk of adverse health events such as stroke, heart attack, heart failure, and death. Lowering BP with drugs has been shown to reduce the risk of these serious health events but the optimal BP target when treating older adults is not known.

Study characteristics

We systematically retrieved all randomised trials that compared the effect of a higher BP target (upper BP number less than 150 to 160 mmHg) with a conventional lower BP target (upper BP number less than140 mmHg) in people over the age of 65 years. The evidence is current to February 2017.

Key results

We found three randomised trials (the 'gold standard' of medical evidence) that investigated this question in a total of 8221 older adults (average age 75 years, 59% female). We did not find a difference between the higher BP target and the conventional lower BP target, however an important difference favoring the lower BP target could not be ruled out.

Quality of the evidence

We judged the pooled evidence to be of low-quality and not able to adequately answer the question as to which target BP was better. More good-quality trials addressing this question are needed.

Summary of findings for the main comparison. Higher BP target (< 150-160/95-105 mmHg) compared with lower BP target (< 140/90 mmHg) for cardiovascular risk reduction

Higher BP target (< 150-160/95-105 mmHg) compared with lower BP target (< 140/90 mmHg) for cardiovascular risk reduction

Patient or population: older adults with primary hypertension

Settings: outpatient

Intervention: higher BP target < 150-160)/95-105 mmHg

Comparison: lower BP target < 140/90 mmHg

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Lower BP target	Higher BP target				
All-cause mortality Mean follow-up: 2.6 years	**31 per 1000**	**39 per 1000** (31 to 48)	**RR 1.24** (0.99 to 1.54)	8221 (3)	⊕⊕⊖⊖ Low[2,3]	
Stroke Mean follow-up: 2.6 years	**20 per 1000**	**25 per 1000** (19 to 33)	**RR 1.25** (0.94 to 1.67)	8221 (3)	⊕⊕⊖⊖ Low[2,3]	
Cardiovascular serious adverse events Mean follow-up: 2.6 years	**42 per 1000**	**50 per 1000** (41 to 61)	**RR 1.19** (0.98 to 1.45)	8221 (3)	⊕⊕⊖⊖ Low[2,3]	
Withdrawals due to adverse effects Mean follow-up: 2.4 years	**17 per 1000**	**14 per 1000** (10 to 20)	**RR 0.83** (0.58 to 1.19)	7497 (2)	⊕⊕⊖⊖ Low[2,3]	

The basis for the **assumed risk** is provided in footnote below. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BP: blood pressure; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

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[1]Rationale for our choice of **assumed risk**: the risk of cardiovascular events in a hypertensive general population varies considerably across countries (Finegold 2013). With no reason to favour one country over another we have opted to use (now and for future updates) an assumed risk, which is the average across studies included in this review.
[2]Downgraded due to high risk of bias.
[3]Downgraded due to heterogeneity and imprecision.

BACKGROUND

Description of the condition

Hypertension (elevated blood pressure (BP)) is a common condition and the second most frequent reason for visiting a family physician in Canada (Chan 2005). Although hypertensive individuals are generally asymptomatic, high BP is associated with higher rates of cardiovascular morbidity and mortality in the population at large (Lewington 2002) and it has been well demonstrated that lowering BP with antihypertensive drugs can reduce cardiovascular morbidity and mortality (Musini 2009; Wright 2009) in people with moderate to severe hypertension. Hence primary care visits for hypertension focus on prevention (lowering overall cardiovascular risk) and frequently involve the adding or adjusting of antihypertensive medication to obtain BPs in a range believed to put the patient at lowest risk for adverse health outcomes.

By convention the target BP for the treatment of otherwise healthy adults is the same as the threshold used to diagnose hypertension (i.e. a target BP less than 140/90 mmHg). Yet the risk and benefit of antihypertensive therapy can be expected to vary across patient populations. In people over the age of 80 years, for example, the evidence for a mortality benefit from BP lowering is conflicting (Beckett 2008; Musini 2009). The BP target that will minimise adverse events in older adults is unknown.

Eight out of 10 major antihypertensive trials in elderly people targeted a systolic BP of less than 160 mmHg (Mancia 2009). These trials (with the exception of the lone trial to target a systolic BP of less than 140 mmHg (JATOS 2008) show improvement in clinical endpoints and lend support to a systolic BP target for older adults of less than 160 mmHg. However a BP target of less than 140/90 mmHg is commonly applied to all people, irrespective of age and, according to a consensus document prepared by the American College of Cardiology Foundation and the American Heart Association, use of this lower BP target in older adults is based only on expert opinion and not on data from randomised controlled trials (RCTs) (Aronow 2011). By performing this review we hope to determine, for older adults, whether differences in BP targets lead to important differences in clinical outcomes.

Description of the intervention

Physicians tailor the introduction and dosing of BP-lowering medication to a person's BP readings. Such readings can be obtained from automated 24-hour ambulatory BP monitors, several days of recordings from patient-actuated home BP machines or same day measurements in the physician's office (single or multiple readings, acquired either by a healthcare worker or an automated device). In practice BP targets (though not based on evidence) may vary with the setting in which BP is measured (e.g. home BP targets may be 5 mmHg lower) and may focus on systolic BP, diastolic BP, or both (Daskalopoulou 2012).

For the purpose of this review we compared a higher (intervention) systolic or diastolic BP target of less than 150 to 160/95 to 105 mmHg to a lower (control) BP target of less than 140/90 mmHg irrespective of how BP was measured.

How the intervention might work

The elderly are a distinct population with greater comorbidity, more polypharmacy, and greater potential risk from low organ perfusion pressure (e.g. cognitive impairment, or postural hypotension resulting in falls and fractures) (Hilmer 2007). More aggressive BP targets mean more medication use and greater potential for adverse drug-drug and drug-disease interactions (Cadieux 1989).

Occlusive vascular disease can also be expected to be more common in the elderly. Conceivably, in people with focal obstructions in blood flow, a reduction in overall BP may further compromise the perfusion, performance and health of that already under-perfused organ - increasing the potential for adverse effects beyond what is seen in typical clinical trial populations (which are generally comprised of younger and healthier participants) (Masoudi 2003; Van Spall 2007).

Cohort studies lend support to speculation that older adults may do better with less aggressive BP targets. In particular, adults over the age of 85 years have been shown to have slower rates of cognitive and physical decline when systolic BP is higher (Sabayan 2012) and the frailest older adults (as measured by gait speed) have lower mortality when hypertension is present (Odden 2012). Such studies have multiple potential explanations but one of these explanations is that the risk/benefit ratio of antihypertensive treatment may be different in the elderly - with maximum overall benefit occurring when less aggressive antihypertensive therapy is pursued and somewhat higher BPs are achieved.

Why it is important to do this review

Given how common the treatment of hypertension is, given our aging population, and given how poorly represented older adults are in most of the large RCTs that guide clinical practice, it is important to explore whether older adults might do just as well, or better, with less aggressive pharmacotherapy for hypertension.

OBJECTIVES

To assess the effects of a higher BP target compared to a lower BP target of less than 140/90 mmHg in hypertensive adults 65 years of age or older.

METHODS

Criteria for considering studies for this review

Types of studies

Open-label RCTs (including parallel-group or cross-over trials) of at least one year's duration. As it is necessary for clinicians to know the BP target to which a patient is randomised in order to adjust their medication, it is assumed that any existing trials will not blind the participant or the care provider.

Types of participants

Adults 65 years of age or older who are either:

1. already being treated for hypertension; or
2. have elevated BP (BP 140/90 mmHg or higher) documented in a standard way on at least two occasions.

Types of interventions

A higher systolic or diastolic BP treatment target (whether ambulatory, home, or office measurements) in the range of systolic BP less than 150 to 160 mmHg or diastolic BP less than 95 to 105 mmHg. Valid comparators would include any BP treatment target that is less than 140/90 mmHg or lower.

Types of outcome measures

Primary outcomes

1. All-cause mortality
2. Stroke (fatal and non-fatal, excluding transient ischaemic attack)
3. Institutionalisation (i.e. nursing home admission)
4. Cardiovascular serious adverse events, including: cerebrovascular disease (infarction, haemorrhage, transient ischaemic attack), cardiac disease (myocardial infarction, new treatment for angina or congestive heart failure, sudden death), vascular disease (enlarging or rupturing or dissecting aneurysms of the aorta, treatment for occlusive arterial disease) and renal failure (acute or chronic doubling of serum creatinine or dialysis)

We chose the first three outcomes because we believe death (from any cause) and disability/loss of independence to be the most important outcomes from the perspective of older adults. We chose our fourth outcome because we believe a composite measure of serious cardiovascular events would have the greatest statistical power to show a difference between therapies.

Secondary outcomes

1. Cardiovascular mortality
2. Non-cardiovascular mortality
3. Unplanned hospitalisation
4. Each component of 'cardiovascular serious adverse events' separately
   a. cerebrovascular disease
   b. cardiac disease
   c. vascular disease
   d. renal failure
5. Total serious adverse events (death, hospitalisation and/or events requiring medical treatment)
6. Total minor adverse events (symptoms not requiring medical treatment such as cough, fatigue or light-headedness)
7. Withdrawals due to adverse effects
8. Systolic BP achieved (mean)
9. Diastolic BP achieved (mean)

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist conducted systematic searches in the following databases for RCTs without language, publication year or publication status restrictions:

1. the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 3 February 2017);
2. the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) via the Cochrane Register of Studies (CRS-Web) (searched 3 February 2017);
3. MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 3 February 2017);
4. Embase Ovid (searched 3 February 2017);
5. ClinicalTrials.gov (www.clinicaltrials.gov) searched 3 February 2017);
6. World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch) searched 3 February 2017).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the sensitivity and precision-maximising strategy designed by Cochrane for identifying randomised controlled trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.d. (Lefebvre 2011)). Search strategies for major databases are provided in Appendix 1.

Searching other resources

We checked all references in the relevant identified trials and attempted to contact the study authors to identify any additional published or unpublished data. We also searched ICTRP in an attempt to uncover unpublished trials; searched ISI Web of Science for papers citing the studies included in this review; and contacted the Food and Drug Administration (FDA) to ask if they had any related clinical trial information in their possession.

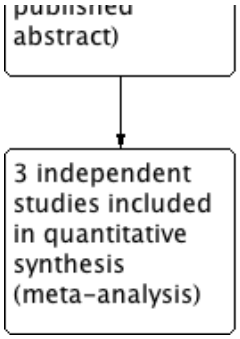
Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of all articles identified by the search algorithm, obtained the full text of all potentially relevant studies and determined which studies met the inclusion criteria. A third author adjudicated any disagreements regarding study inclusion. A full accounting of the search results is provided in Figure 1 in the form of a PRISMA study flow diagram (Liberati 2009).

Figure 1. Study flow diagram

Figure 1. (Continued)



Data extraction and management

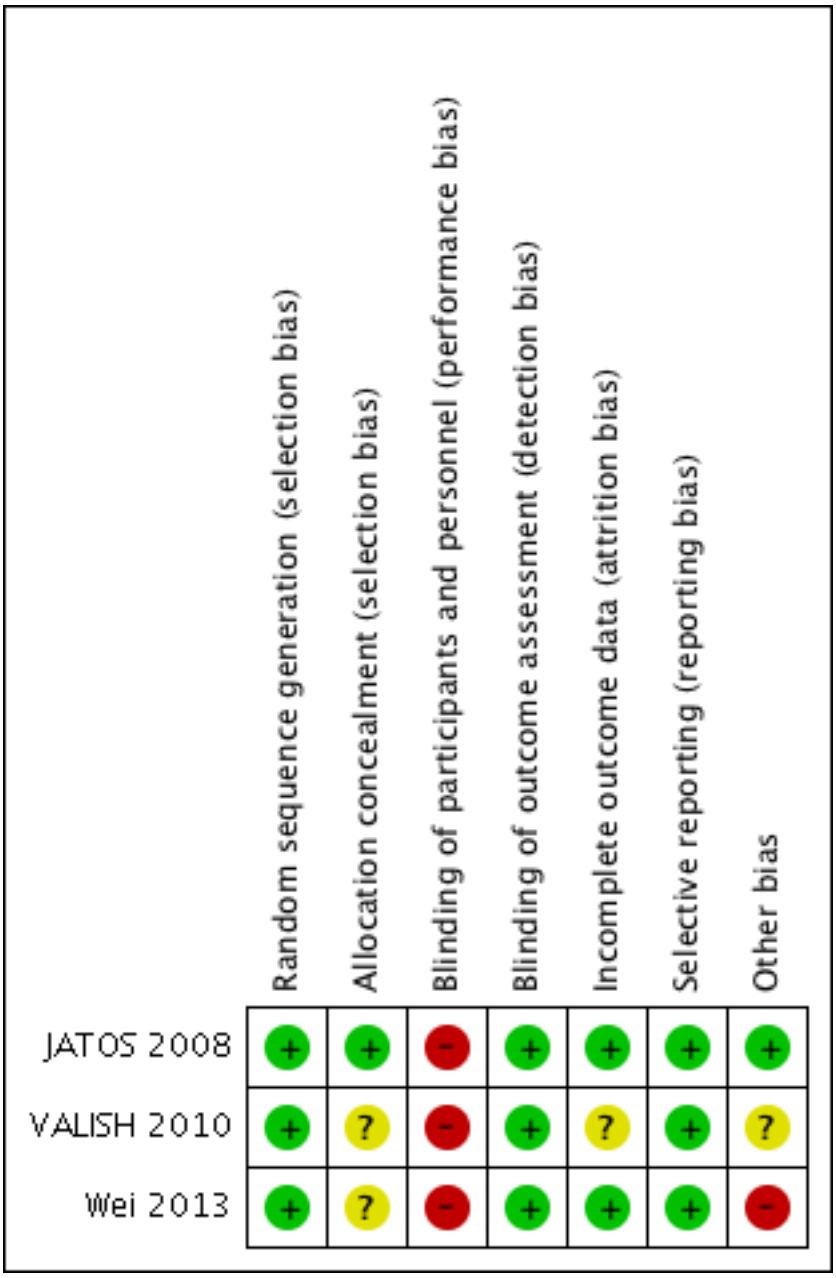
Two review authors independently extracted data onto specially designed forms. One review author entered the data into Review Manager 5 (RevMan 5) software (RevMan 2014) and a second review author independently checked the data entry.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies using the Cochrane recommended tool (Higgins 2011). A third review author adjudicated any disagreements.

We assessed the risk of bias for each study according to six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other sources of bias'. We rated each domain as high, low or unclear risk of bias. We presented the risk of bias assessment in a table for each study, and provided a graph displaying risk of bias across studies and domains, respectively (Figure 2).

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



Measures of treatment effect

We measured most of our outcomes as the proportion of participants suffering an event. This includes mortality (all-cause, cardiovascular, non-cardiovascular), stroke, institutionalisation, total serious adverse events, cardiovascular serious adverse events and its individual components, total minor adverse events, withdrawals due to adverse effects, and unplanned hospitalisation. For achieved systolic and diastolic BPs we used the intervention and control group means.

Unit of analysis issues

For each included study the unit of analysis and the unit of randomisation (expected to be the participant) needed to match to prevent the introduction of bias. For any study in which this was not the case, our intention was to qualitatively describe the findings but not include such studies in meta-analyses. For all included studies the unit of analysis and the unit of randomisation matched.

Dealing with missing data

We attempted to contact authors of included studies for any necessary clarification, and to request any missing data. If data were still missing after author contact, and assumed to be missing at random (i.e. provided it appeared that the reason data were missing had nothing to do with the data values themselves) then our intention was to analyse only available data. If we believed that persistently missing data were missing for non-random reasons, then our intention was to impute values for these missing data using methods such as assigning a poor value to each, assigning the

mean value, or using the last value carried forward. The decision on how to impute such values was to depend on what was missing, and on the study design. No missing values were identified for which these steps were needed.

Assessment of heterogeneity

We assessed heterogeneity using a Chi^2 test on n-1 degrees of freedom and by calculating the I^2 statistic (Higgins 2003). Where statistical heterogeneity was found we examined the trial methodology, the intervention, and the study populations with an eye to finding potential explanations for observed variation (Deeks 2011). Subgroup analysis was not possible as this information was not available for the included trials.

Assessment of reporting biases

We did not prepare any funnel plots as we only identified three studies (we had previously stated in the protocol that such a graph would be produced if 10 or more studies were found).

Data synthesis

We combined trial data identified for inclusion in this review using the most current version of the Cochrane statistical package, RevMan 5 (RevMan 2014). We anticipated a similar magnitude of effect across studies and accordingly performed only fixed-effect meta-analyses.

Subgroup analysis and investigation of heterogeneity

None of the three included trials reported outcomes in a way that permitted subgroup analysis. As stated in our protocol, when possible, we intended to use subgroup analysis to search for variation in treatment effect and to explore possible sources of heterogeneity. Prespecified subgroups related to clinical presentation included gender, age (under/over 75 years), and frailty (via a median split of either integrative physical measures such as gait speed or of composite clinical frailty scores). Prespecified subgroups related to method of treatment included the class of medication with which the treatment protocol began (e.g. calcium channel blocker versus angiotensin receptor blocker (ARB)). Although we identified that we may perform additional subgroup analyses we stated that such post-hoc analyses would be merely hypothesis-generating.

Sensitivity analysis

Where heterogeneity existed, we presented results both with and without the outlying trial(s). Where high risk of bias existed, we presented results both with and without the high-risk trial(s).

RESULTS

Description of studies

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

Results of the search

A search of the Database of Abstracts of Reviews of Effects (DARE) revealed no prior reviews specific to BP targets in older adults. Search results from the Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE, MEDLINE In-Process, Embase, and ClinicalTrials.gov revealed 1669 citations (3088 prior to deduplication). We screened titles and abstracts for all 1669 citations. Of these, the review authors obtained and reviewed 24 full papers. We excluded 13 studies (see Characteristics of excluded studies) and 2 potentially eligible studies were ongoing (see Characteristics of ongoing studies). Of the remaining nine publications, only three were independent RCTs meeting our inclusion criteria. The other six publications were derived from these three RCTs in some way (one protocol, one protocol that included participant characteristics and BP results in the first year, three substudies, and one previously published abstract) (Characteristics of included studies). Contacting the FDA, searching ISS Web of Science for papers citing the studies included in this review, and a search of the International Clinical Trials Registry Platform (WHO-ICTRP) revealed no additional published or unpublished studies.

Included studies

The two larger of the three included trials (4418 and 3079 participants in analysis) were in Japanese outpatients with either systolic hypertension irrespective of diastolic BP (JATOS 2008) or isolated systolic hypertension (VALISH 2010). These participants were in their mid 70s, and had baseline BPs of 170/90 (JATOS 2008) and 170/81 (VALISH 2010). Around 61% of these participants were women, around 12% had diabetes and around 16% smoked. The smaller trial (724 participants in analysis) enrolled Chinese general practice patients with either systolic or diastolic hypertension (Wei 2013). Mean baseline BP was 160/84 mmHg and these participants differed from the Japanese trials in being predominantly men (66%) with twice as many people with diabetes (23%) and more that smoked (25%).

The two Japanese trials compared conventional systolic BP targets of less than 140 mmHg to higher systolic targets of less than 150mmHg (VALISH 2010) or less than 160 mmHg (JATOS 2008). The Chinese trial compared a conventional strict mixed systolic and diastolic BP target of less than 140/90 mmHg to less than 150/90 mmHg (Wei 2013). Achieved BP was similar in the lower BP groups for all three trials (around 136/75 at study conclusion) but achieved BP differed substantially in the higher BP group, being 142/76.5 mmHg in VALISH 2010, 145.6/78.1 in JATOS 2008, and 149.7/82.1 in Wei 2013.

In two of the trials the study protocol mandated that participants be initially switched to, or started on (if previously untreated), a specified study medication. These medications were either the long-acting dihydropyridine calcium antagonist efonidipine (JATOS 2008) or the angiotensin II type 1 receptor blocker valsartan (VALISH 2010). In Wei 2013 it is unclear how the initial choice of medication was made but could include single drug treatment of either an angiotensin-converting-enzyme (ACE) inhibitor (enalapril), a beta-blocker (bisoprolol or metoprolol), a calcium channel blocker (amlodipine), or a diuretic (indapamide). In all three studies drug doses were adjusted upwards and numbers of drugs increased until BP control was achieved according to the allocated BP target. Trial protocols led to all JATOS 2008 subjects being on efonidipine with 36% of these subjects also receiving an ACE/ARB (plus 13% received a betablocker and 12% received a diuretic). VALISH 2010 subjects all took valsartan, with 37% also taking a calcium channel blocker (plus 12% taking a diuretic and 5% taking a betablocker). Wei 2013 subjects were more balanced as to use of different antihypertensive classes (ACEI 31%, calcium channel blocker 28%, beta blocker 20%, diuretic 20%).

All three studies were prospective, randomised, parallel, and open-label with average follow-up ranging from two years (JATOS 2008) to four years (Wei 2013). All studies used a primary outcome that was a composite of major adverse cardiovascular events and all composites included fatal and nonfatal stroke and myocardial infarction, and death from other cardiovascular causes (sudden death, congestive heart failure). The two Japanese trials also included within the composite other hospitalisations for cardiovascular disease (e.g. angina, aortic dissection) and renal dysfunction.

Excluded studies

In all cases, we excluded studies because they were not randomised trials using the conventional and relaxed BP targets identified for this review.

Risk of bias in included studies

We carried out the 'Risk of bias' assessment as outlined in the methods and summarised our assessments in Figure 2.

Allocation

The risk of allocation bias was unclear in two of the trials (VALISH 2010 and Wei 2013) largely because of inadequate description in the methods.

Blinding

We rated the risk from blinding high for all three trials, since neither clinicians nor participants could be blinded to the allocated BP target. However outcome assessors were blinded, which mitigates concerns to some degree.

Incomplete outcome data

Although it was generally unclear how participants who were lost to follow-up were handled in the analysis, all trials had fairly low rates of attrition. The highest rate of attrition was in VALISH 2010 (5.9%), which we rated at unclear risk of bias because more participants dropped out than experienced the primary outcome and no sensitivity analysis was performed.

Selective reporting

Although we rated all trials as low risk of reporting bias for their identified primary and secondary outcomes, Wei 2013 did not provide total serious adverse events and reported adverse events only selectively.

Other potential sources of bias

We rated VALISH 2010 at unclear risk of bias because it did not describe how participants were selected for a per-protocol analysis (with participants excluded "...according to a judging criteria drawn up by the Statistical Committee of this study"). We rated Wei 2013 as high risk of bias because an initial analysis of this study was published in abstract form with no mention of Wei (the lead author of the final publication) as a co-investigator. E-mail communication with authors of Wei 2013 confirm that the lead author was a late addition to the project and hence, in our view, unable to meaningfully take responsibility for study design and conduct.

Effects of interventions

See: **Summary of findings for the main comparison** Higher BP target (< 150-160/95-105 mmHg) compared with lower BP target (< 140/90 mmHg) for cardiovascular risk reduction

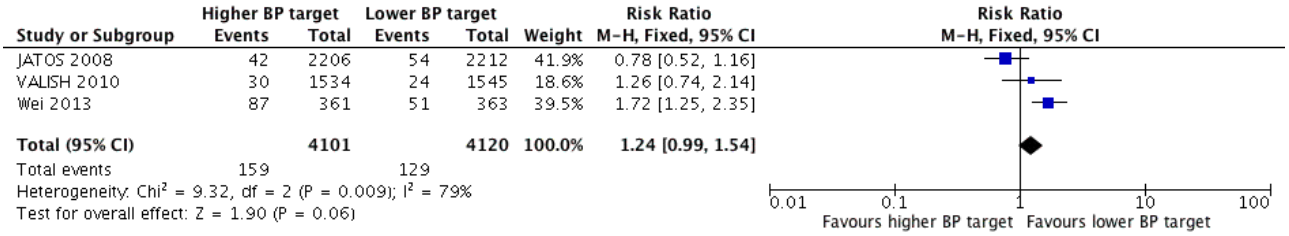
See: Summary of findings for the main comparison

Primary Outcomes

1. All-cause mortality

Although all three studies provided data on total mortality, only results from Wei 2013 were statistically significant, finding the higher BP target to be inferior (RR 1.72, 95% CI 1.25 to 2.35). In contrast, JATOS 2008 found a non-significant difference in the opposite direction, favouring the lower target (RR 0.78, 95% CI 0.52 to 1.16). Pooling data produced a nonsignificant difference (RR 1.24, 95% CI 0.99 to 1.54) with high heterogeneity (I^2= 79%) (Figure 3, Analysis 1.1).

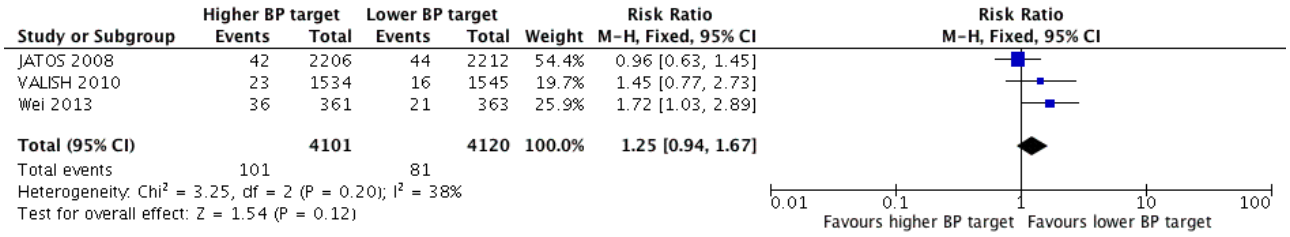
Figure 3. Forest plot of comparison higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, outcome 1. All-cause mortality.



2. Stroke (fatal and non-fatal, excluding transient ischaemic attack)

All three studies provided data on stroke and only results from Wei 2013 were statistically significant, finding the higher BP target to be inferior. Pooling data produced a nonsignificant difference (RR 1.25, 95% CI 0.94 to 1.67) with moderate heterogeneity (I^2 = 38%) (Figure 4, Analysis 1.2).

Figure 4. Forest plot of comparison higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, outcome 2. Stroke



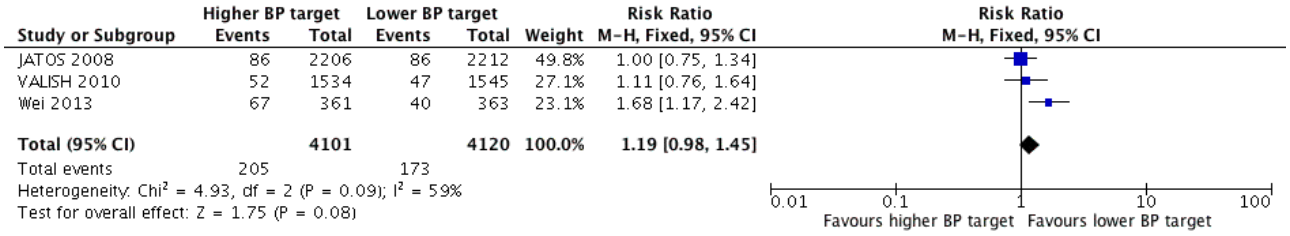
3. Institutionalisation (i.e. nursing home admission)

Although we believe this to be an important outcome for older adults it was not reported in any of the included studies.

4. Cardiovascular serious adverse events (cerebrovascular disease, cardiac disease, vascular disease and renal failure)

All three studies provided data on cardiovascular serious adverse events and only Wei 2013 was statistically significant, finding the higher BP target to be inferior. Pooling data produced a nonsignificant difference (RR 1.19, 95% CI 0.98 to 1.45) with high heterogeneity (I^2 = 59%) (Figure 5, Analysis 1.3).

Figure 5. Forest plot of comparison higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, outcome 4. Cardiovascular serious adverse events



Secondary Outcomes

1. Cardiovascular mortality

All three studies provided data on cardiovascular mortality and only results from Wei 2013 were statistically significant, finding the higher BP target to be inferior. Pooling data produced a statistically significant difference showing the higher target to be inferior (RR 1.52, 95% CI 1.06 to 2.19) with high heterogeneity (I^2 = 52%) (Figure 6, Analysis 1.4).

Figure 6. Forest plot of comparison higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, outcome7. Withdrawals due to adverse effects

2. Non-cardiovascular mortality

All three studies provided data on non-cardiovascular mortality and none demonstrated statistically significant differences. Pooling data produced a non-significant difference (RR 1.09, 95% CI 0.81 to 1.46) with high heterogeneity (I^2 = 52%) (Analysis 1.5.)

3. Unplanned hospitalisation

Only VALISH 2010 reported unplanned hospitalisation and no significant difference was found (RR 1.18, 95% CI 0.55 to 2.53) (Analysis 1.6).

4. Cardiovascular serious adverse events

4a. Cerebrovascular disease (infarction, haemorrhage or transient ischaemic attack)

All three studies provided data on cerebrovascular disease and only results from Wei 2013 were statistically significant, finding the higher BP target to be inferior. Pooling data produced a non-significant difference (RR 1.22 95% CI 0.93 to 1.61) with moderate heterogeneity (I^2 = 46%) (Analysis 1.7.1).

4b. Cardiac disease (myocardial infarction, new treatment for angina or congestive heart failure, sudden death)

All three studies provided data on cardiac disease and only results from Wei 2013 were statistically significant, finding the higher BP target to be inferior. Pooling data produced a non-significant difference (RR 1.21, 95% CI 0.82 to 1.79) with no heterogeneity (I^2 = 0%) (Analysis 1.7.2). Differences between groups were largely accounted for by congestive heart failure.

4c. Vascular disease (enlarging or rupturing or dissecting aneurysms of the aorta, treatment for occlusive arterial disease)

Only one study provided information on vascular disease (JATOS 2008) and found a non-significant difference (RR 2.01, 95% CI 0.37 to 10.94) (Analysis 1.7.3).

4d. Renal failure (acute or chronic doubling of serum creatinine or dialysis)

Only two studies provided information on renal failure (JATOS 2008, VALISH 2010) and neither demonstrated significant differences. Pooling data produced no significant difference (RR 0.85, 95% CI 0.38 to 1.89) with low heterogeneity (I^2 = 12%) (Analysis 1.7.4).

5. Total serious adverse events (death, hospitalisation and/or events requiring medical treatment)

Only VALISH 2010 reported total serious adverse events, which showed no significant difference (RR 0.93, 95% CI 0.69 to 1.24) (Analysis 1.8).

6. Total minor adverse events (symptoms not requiring medical treatment such as cough, fatigue or light-headedness)

Only two studies provided information on total minor adverse events (JATOS 2008, VALISH 2010) and neither demonstrated significant differences. Pooling data produced no significant difference (RR 0.99, 95% CI 0.91 to 1.08) with low heterogeneity (I^2 = 0%) (Analysis 1.9).

7. Withdrawals due to adverse effects

Only two studies provided information on withdrawals due to adverse effects (JATOS 2008, VALISH 2010) and neither demonstrated significant differences. Pooling data produced no significant difference (RR 0.83, 95% CI 0.58 to 1.19) with moderate heterogeneity (I^2 = 36%) (Figure 6, Analysis 1.10).

8. Systolic BP achieved (mean difference)

Pooling all three studies, the mean difference in achieved systolic BP was 8.88 mmHg (95% CI 8.38 to 9.39 mmHg) greater in the higher as compared to the lower BP target groups with high heterogeneity (I^2 = 98%) (Analysis 1.11).

9. Diastolic BP achieved (mean difference)

Pooling all three studies, the mean difference in achieved diastolic BP was 3.09 mmHg (95% CI 2.72 to 3.47 mmHg) greater in the higher as compared to the lower BP target groups with high heterogeneity (I^2 = 96%) Analysis 1.12.

DISCUSSION

Overview

Three relatively large RCTs met our inclusion criteria, however we rated the quality of evidence for our pooled estimates of effect as low for all outcomes. In most cases this downgrade was because of high heterogeneity and imprecision. In some cases we downgraded the quality of evidence because of high risk of bias or because not all trials reported the outcome of interest.

How were these studies heterogeneous?

One of the three included trials (Wei 2013: 724 participants) was substantially smaller than the other two trials (JATOS 2008: 4418 participants; VALISH 2010: 3079 participants) but none of the three trials dominated the weight of the analysis because the smallest trial (Wei 2013) had much higher event rates. This is at least partially explained by the fact that Japan (where the two larger trials took place) has one of the lowest age-standardised cardiovascular mortality rates in the world and China (where Wei 2013 was conducted) has an indirectly standardised mortality ratio for ischaemic heart disease which is four times higher than Japan (and marginally higher than the USA) (Finegold 2013). Although the methods in Wei 2013 did not describe attempts to select a higher risk population, the composite primary outcome event rate in the less-than-140 mmHg-BP group of Wei 2013 (which we calculate to be 2.8% per year) was not that different than the composite cardiovascular event rate in the 75-years-or-over subset of the recently completed SPRINT trial's less-than-140 mmHg arm (which we calculate to be 3.3% per year) (SPRINT 2015). SPRINT participants were Americans without diabetes, considered to be at high risk of cardiovascular disease.

Separate from the difference in the underlying event rates, these three trials found very different estimates of the direction and magnitude of effect. With only three studies to compare, it is difficult to consider any one trial an outlier. One study (VALISH 2010) found nonsignificant results that most often lay between the other two studies. These other two studies either statistically significantly favoured the lower BP target for many outcomes (Wei 2013) or found a nonsignificant difference that lay close to, and at times even on the opposite side of, the no-effect line (JATOS 2008). Selectively excluding JATOS 2008 from the meta-analysis removed the heterogeneity for all-cause mortality (I^2 79% →0%) and stroke (I^2 38% →0%), while removing Wei 2013 removed the heterogeneity from cardiovascular serious adverse events (I^2 59% →0%) and cardiovascular mortality (I^2 52% →0%).

An exploration of the observed heterogeneity

Methodology

Although the methodology described in each trial was not sufficiently different to explain the observed heterogeneity, we considered the only trial reporting a statistically significant benefit (Wei 2013) to be at high risk of bias, because the lead author appeared to join the trial after the results had already been reported in a conference abstract. When we excluded Wei 2013 from the analysis, all trends towards a benefit for the lower target disappeared. In particular this included all-cause mortality (RR 0.93, 95% CI 0.68 to 1.27), cardiovascular serious adverse events (RR 1.04, 95% CI 0.82 to 1.32), and cardiovascular mortality (RR 0.90, 95% CI 0.48 to 1.71).

Populations studied

Consistent with the observed differences in event rates between these trials, participants in Wei 2013 had substantially higher prevalence of cardiovascular risk factors than did participants in JATOS 2008. Specifically, Wei 2013 had a higher proportion of men (66% versus 40%), higher proportion of people with diabetes (23% versus 12%), higher proportion of people that smoked (25% versus 13.5%), and greater age (76.5 years versus 73.6 years). The discussion in Wei 2013 also offered other information on baseline characteristics compared to JATOS 2008 that were not included in the body of the text (all of which showed Wei 2013 participants to be at higher risk) including differences in prior stroke (6.9% versus 4.2%), prior coronary heart disease (7.5% versus 3%), and presence of atrial fibrillation (18% in Wei 2013, excluded in JATOS 2008).

Outcomes

It is important to note that the primary outcome in Wei 2013 was driven by differences in stroke and congestive heart failure (fatal and non-fatal). Fatal and non-fatal myocardial infarction, in contrast, was essentially identical for both BP targets in all three trials. Importantly, and separate from the relative benefit of the different BP targets, coronary events (which typically represent a large proportion of events in trials with younger, high cardiovascular-risk, hypertensive populations) represented a minority of events in these three trials of older, hypertensive adults (Wei 2013 18/107 events = 16.8% of events were myocardial infarction; JATOS 2008 31/176 events = 17.6% of events were myocardial infarction or angina; VALISH 2010 9/99 events = 9.1% of events were myocardial infarction). The HYVET antihypertensive trial (Beckett 2008) in people over the age of 80 years, similarly found both stroke and congestive heart failure to be more frequent occurrences than myocardial infarction (fatal or nonfatal outcomes in the placebo group were: stroke 17.7%, heart failure 14.8%, myocardial infarction only 3.1%). This compares, for instance, to the ACCOMPLISH trial (Jamerson 2008) which compared benazepril plus amlodipine to benazepril plus hydrochlorothiazide. In this often-cited trial of (relatively) younger, high-risk, hypertensive adults (average age 68.4 yrs) coronary revascularisations accounted for 720/1231 = 58.5% of the composite primary outcome. Chronic disease surveillance carried out by the Canadian government is consistent with this age differential in cardiovascular events. Examining (and stratifying by age) hospitalisations for coronary artery disease, congestive heart failure and stroke in Canada, the majority of such admissions (78.2%) are for coronary artery disease in the 55 years to 65 years age group whereas coronary artery disease accounts for only 38.8% of such admissions in those over 85 years of age (Dai 2009).

Intervention

Two aspects of the intervention are likely to be relevant to the observed differences in trial results. The first is the difference in systolic BP in the lower BP target group, compared to the higher BP target group (-14.0 mmHg in Wei 2013, -9.7 mmHg in JATOS 2008, -5.4 mmHg in VALISH 2010). Clearly the greater difference in BP between treatment arms in Wei 2013 could explain some of the difference in the degree of benefit seen. The other potentially important difference is in which medications were used. In JATOS 2008 (the trial that concluded no difference between BP targets), all participants initially started and continued to use the calcium channel blocker efonidipine and had other medications added if needed. Roughly half of the participants in this trial were on efonidipine as monotherapy. The most common add-on medications in the lower BP group included ACEI/ARB (40.7% of participants), followed distantly by adrenoceptor-blocking drugs (14.3%) and diuretics (15.3%). The heavy reliance on calcium channel blockers is important since they have been demonstrated in meta-analysis to be inferior to other antihypertensives in preventing heart failure outcomes (Chen 2010; Ettehad 2016). In VALISH 2010 (the trial that reported a nonsignificant trend to benefit for the lower BP target) all participants initially started on the ARB, valsartan. Roughly 57% were on valsartan monotherapy with the most commonly added agents in the lower BP target group again being calcium channel blockers (37.1%), followed much more distantly by diuretics (13.0%) and beta-blockers (6.0%). In contrast Wei 2013 (the trial demonstrating statistically significant benefit) started participants on a variety of medications and ended up with the lower BP target group having participants on the ACE inhibitor, enalapril (31.5%), the calcium channel blocker amlodipine (27.2%), the beta-blockers metoprolol or bisoprolol (21.2%) and the diuretic, indapamide (21.2%). Although it is not stated how many participants were on monotherapy with each agent, we know from VALISH 2010 and JATOS 2008 that roughly 50% of participants ended up on monotherapy with one drug. Given the greater BP difference in this trial, the percentage of participants on monotherapy may be even smaller. If so, and if participants started on each drug class equally frequently, we estimate only 12% of Wei 2013 participants to have been on monotherapy with a calcium channel blocker.

Possible explanations for the observed heterogeneity

1. Bias may have influenced the sole trial finding a statistically significant benefit. We considered Wei 2013, the smallest trial driving any trend to benefit, to be at high risk of bias.
2. The effect of antihypertensive medication on outcomes that are common in the elderly may differ by medication class. The older adults participating in these three trials had stroke and heart failure (fatal and nonfatal) as their most common cardiovascular events. Each trial also differed in the extent to which they relied on medications indicated for use in heart failure. In Wei 2013 (the single study finding statistically significant benefit) close to 90% of participants were expected to have been on at least one, and possibly two or more drugs with established benefit to treat or prevent heart failure. In JATOS 2008 (the study finding no benefit) roughly half of these participants were on monotherapy with a calcium channel blocker, a medication class shown to be inferior to other antihypertensives for preventing heart failure outcomes (Chen 2010, Ettehad 2016). It is conceivable that the heavy reliance of JATOS 2008 on a calcium channel blocker might have led to less effective risk reduction for heart failure-related events, which were one of the main contributors to the composite primary outcome in all three studies. The substantially more common cardiovascular risk factors in Wei 2013, including the 18% of participants with atrial fibrillation (which JATOS excluded), would also be expected to put the participants in Wei at substantially greater risk of stroke than those of JATOS 2008. Although calcium channel blockers have superior efficacy to other antihypertensives for the prevention of stroke (Chen 2010, Ettehad 2016), the low-risk participants in JATOS 2008, and the relatively smaller difference in BP between study arms in that trial, may have diminished the opportunity for stroke benefit to be seen.

Summary of main results

See Summary of findings for the main comparison for key results. Although none of our primary outcomes reached conventional statistical significance, two of these outcomes were numerically in favour of the lower BP target, these being all-cause mortality (RR 1.24, 95% CI 0.99 to 1.54) and cardiovascular serious adverse events (RR 1.19, 95% CI 0.98 to 1.45). Consistent with the possibility that these differences might be real, cardiovascular mortality also favoured the lower BP target and was statistically significantly different (RR 1.52, 95% CI 1.06 to 2.19). Although this suggests the potential of a clinically important difference favouring the lower BP target, the high degree of unexplained heterogeneity amongst these trials (I^2 of 38% to 79% for the primary outcomes), and the apparent disappearance of potential benefit when the single trial considered to be at high risk of bias was removed, prevents any conclusions being drawn.

Overall completeness and applicability of evidence

In this review we systematically searched all relevant electronic databases. It is unlikely that published RCTs meeting our inclusion criteria would have been missed, however unpublished studies could have gone undetected. There were too few studies to assess the likelihood of missing studies with a funnel plot. The study participants appear to have all been drawn from general practice populations, however these populations may have been somewhat atypical for general practice patients in many countries given that they appeared to be either at lower risk than average for cardiovascular events (JATOS 2008 and VALISH 2010), or higher risk than average (Wei 2013).

Quality of the evidence

We assessed the risk of bias for each of the RCTs included in this review (Figure 2), and we viewed one of the three included trials as having a higher overall risk of bias. While two large RCTs and one moderate-sized RCT might normally be considered to provide high-quality evidence, the high level of heterogeneity observed, and the higher potential for bias in the only trial finding benefit, led us to consider this evidence as low quality overall.

Potential biases in the review process

This review is limited to published trials. Conceivably smaller trials that were never published might exist (publication bias). The high heterogeneity also suggests that either Wei 2013 or JATOS 2008 may substantially over, or under-estimate, the magnitude of the mean benefit conveyed by differing BP targets.

Agreements and disagreements with other studies or reviews

SPRINT 2015, an RCT in high cardiovascular disease risk, non-diabetic hypertensive people, comparing a systolic BP target of less than 140 mmHg with less than 120 mmHg, does not meet the inclusion criteria for this review and has been excluded. For the subset of participants over the age of 75 years (2636 subjects, mean age 79.9 years), this trial reported a statistically significant difference in a composite CVD primary outcome that favoured the lower BP target (HR 0.67, 95% CI 0.51 to 0.86). For SPRINT 2015 as a whole, the average difference in BP between treatment groups was 14.8 mmHg. If a difference in BP targets can demonstrate risk reduction when those BPs are already fairly low (as in SPRINT 2015), it seems possible that benefit from a lower BP target might also be found when those targets are substantially higher (as in our review). Multiple systematic reviews (Chen 2010; Ettehad 2016; Wiysonge 2017; Xue 2015) have also demonstrated that antihypertensive drug classes differ in their efficacy for preventing various cardiovascular events. In particular diuretics appear superior at preventing heart failure compared to other drugs, calcium channel blockers appear inferior at preventing heart failure compared to other drugs, and both calcium channel blockers and ARBs appear superior at preventing stroke. Given our observation that heart failure admissions are a major driver of events in older adults, the body of literature suggesting that calcium channel blockers are inferior to other agents for the prevention of heart failure might explain why JATOS 2008 (in which half the subjects were on calcium channel blocker monotherapy) did not find benefit to the lower BP target.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence at present to determine whether a higher systolic blood pressure (BP) target of less than 150 to 160 mmHg, as compared to a lower systolic BP target of less than 140 mmHg, conveys meaningful differences in benefit or harm to older adults with hypertension.

Implications for research

Additional randomised trials examining BP targets in all older adults are needed. However, since much of the concern about excessive BP lowering in older adults revolves around those who are frail, those who have mild cognitive impairment, and those who have a low diastolic BP at baseline, future trials could maximise their clinical utility by measuring and reporting results separately for participants in these important subgroups.

It is also apparent from the studies in our review, and from other studies in older adults like HYVET (Beckett 2008), that the relative frequency of different cardiovascular events varies with age. While coronary artery disease may be the main driver of cardiovascular events in most studies, adverse cardiovascular events in older adults appear driven more by heart failure and stroke. Given that antihypertensive drugs probably differ in their ability to prevent certain types of outcomes, antihypertensive choice in the elderly may differ from that in (relatively) younger people with hypertension. In particular, drugs with a favourable effect on heart failure (such as diuretics) might be preferred over agents that are less effective against heart failure (calcium channel blockers). Head-to-head trials in the elderly of different drug classes (in particular diuretics and calcium channel blockers), using the agents with the best available evidence for benefit (e.g. chlorthalidone and amlodipine) are also warranted.

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Xue H, Lu Z, Tang WL, Pang LW, Wang GM, Wong GWK, et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD008170.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

JATOS 2008

Methods	PROBE study. Presumably multi-centre (not stated) 4418 randomised and analysed 2212 (lower), 2206 (higher)
Participants	Elderly Japanese outpatients 65-85 years with baseline BP > 160 mmHg Mean 73.6 years, 60% women Baseline BP 170/90, 12% had diabetes mellitus, 55% previous BP treatment, 13.5% smoked **Exclusions**: current use of efonidipine, diastolic BP > 120 mmHg, secondary hypertension, recent stroke (< 6 months prior) or signs and symptoms of stroke, a recent MI or coronary angioplasty (< 6

JATOS 2008 *(Continued)*

	months previously), angina pectoris requiring hospitalisation, CHF (NYHA) ≥ class II, persistent arrhythmia such as atrial fibrillation, dissecting aneurysm of the aorta or occlusive arterial disease, hypertensive retinopathy, serum aspartate aminotransferase or serum alanine aminotransferase levels > double the respective upper limits of normal, poorly controlled diabetes mellitus (fasting blood sugar ≥ 200 mg/dL or HbA1c ≥ 8%), renal disease (serum creatinine ≥ 1.5 mg/dl), malignant disease or collagen disease. People considered "unsuitable as subjects" were also excluded
Interventions	2 years lower BP target (systolic BP < 140 mmHg) versus higher BP target (systolic BP < 160 but ≥ 140 mmHg) Run-in period (4 weeks in untreated participants and 2–4 weeks in treated participants) to assess baseline BP during which participants were examined on at least two occasions Untreated participants initially received efonidipine 20-40 mg once daily (a long-acting dihydropyridine calcium antagonist). In participants who were already receiving antihypertensive medications, a similar dose of efonidipine was added or substituted for one of the drugs being received before study entry without a washout period. Daily dose of efonidipine could be increased to 60 mg (once or twice daily) and antihypertensive drugs other than calcium antagonists were added, if needed Study visits: with physicians every 2 or 4 weeks. During these visits BP drugs were titrated to the allocated target BP with the goal of reaching that achieved BP within 3 months of treatment allocation. Achieved BP at study completion 135.9/74.8 (lower) versus 145.6/78.1 (higher)
Outcomes	The primary endpoint was the combined incidence of cerebrovascular disease (cerebral haemorrhage, cerebral infarction, transient ischaemic attack, and subarachnoid haemorrhage), cardiac and vascular disease (myocardial infarction, angina pectoris requiring hospitalisation, heart failure, sudden death, dissecting aneurysms of the aorta, and occlusive arterial disease), and renal failure (acute or chronic renal failure; doubling of the serum creatinine concentration to a value of 1.5 mg/dL or higher) Cerebrovascular disease was diagnosed based on neurological and radiological examinations. Cardiac and vascular diseases were diagnosed using radiographic, echocardiographic, and biochemical methods in addition to signs and symptoms. Sudden death, defined as death from instantaneous, unanticipated circulatory collapse within 1 h of initial symptoms, was also included in cardiac and vascular disease. Arrhythmias such as atrial fibrillation were not included in the primary endpoint, but were considered adverse events. Secondary endpoints were "deaths from any cause, morbidity other than cardiovascular disease, changes in BP and heart rate, and any problems in regard to safety." All outcomes were assessed at 2 years. Participants who died within 28 days after the onset of any of the primary or secondary endpoints were considered to have died from these diseases.
Notes	**Dates:** the registration period was from 1 April 2001-31 December 2002. The treatment period ended on 31 December 2004. All participants followed for two years **Funding Source:** sponsored by Shionogi & Co Ltd (makers of efonidipine) **Declaration of potential conflicts of interest:** not reported **Other:** supported by the Japan Physicians Association and the Japanese Society of Hypertension collaborators, but did not mention how these organisations are funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned the subject to either treatment group using a computer-generated list
Allocation concealment (selection bias)	Low risk	"The investigators sent a registration form describing the clinical characteristics of eligible patients to the registration office by facsimile. Immediately after registration, the registration office randomly assigned the subject to either

JATOS 2008 *(Continued)*

		treatment group using a computer-generated list and informed the investigators of the treatment assignments."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and clinicians not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint assessment committee was blinded and reasonably objective outcomes were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	An ITT analysis was performed on all randomised participants with the exception of the 1.6% and 1.7% of participants that were lost to follow-up. Unclear how those lost to follow-up were handled in the analysis
Selective reporting (reporting bias)	Low risk	Reporting appears complete
Other bias	Low risk	The study was funded by the makers of efonidipine but the study question and design were not product focused

VALISH 2010

Methods	PROBE study. Multicenter 1545 lower, 1534 higher in analysis (after removing loss to follow-up and those that withdrew)
Participants	Japanese outpatients ≥ 70 and < 85 years with isolated systolic hypertension (systolic BP > 160 mm Hg and diastolic BP < 90 mm Hg) who were either previously untreated or who could be switched from their current medications to valsartan. It is unclear whether only participants that tolerated valsartan were randomised. **Exclusions**: secondary or malignant hypertension, seated systolic BP ≥ 200 mmHg or diastolic BP ≥ 90 mmHg, cerebrovascular disorder or myocardial infarction in the 6 months prior to enrolment, coronary arterioplasty 6 months prior to enrolment or coronary arteriography planned in the 6 months following enrolment, severe heart failure (≥ NYHA functional classification III), severe aortic stenosis or valvular heart disease, atrial fibrillation/flutter or serious arrhythmia, renal dysfunction with a serum creatinine level of ≥ 2 mg/dL, serious liver disease, history of hypersensitivity to valsartan, and "other patients who are judged to be inappropriate for the study by the investigator or subinvestigator". Mean age: 76.1 years. Baseline BP 170/81. 62.4% women, 13.0% had diabetes, 19.2% smoked
Interventions	Blood pressure targets of < 140 (lower) versus 140 to ≤ 150 mmHg (higher) Staged dose adjustments: valsartan, 40-80 mg once daily, was the first-step therapy for all participants. If the target BP in each group was not achieved within 1-2 months, the dose of valsartan was increased (if < 160 mg) and/or other antihypertensive agents (except angiotensin II type 1 receptor blockers) were added. Participants visited the clinic a minimum of once every 3 months for 2 years. 56.1% of lower participants & 57.6% of higher participants received valsartan only. 43.9% of lower participants and 42.4% of higher participants received additional BP meds (most commonly a CCB). Mean medications n = 1.6 for both groups Achieved BP at study completion: 136.6/74.8 (lower) versus 142/76.5 (higher)

VALISH 2010 *(Continued)*

Outcomes	The primary end point of this study was a composite of cardiovascular events: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death because of heart failure, other cardiovascular death, unplanned hospitalisation for cardiovascular disease, and renal dysfunction (doubling of serum creatinine to a level > 2.0 mg per 100 mL or introduction of dialysis). Secondary end points were each component of the primary end point independently, total mortality, and new onset or exacerbation of angina pectoris. Cardiovascular death, fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke excluding transient ischaemic attacks were evaluated as hard end points
Notes	**Dates:** participants were enrolled from February 2004-August 2005 and followed up until March 2008 (median follow-up 3.07 years) **Funding Source:** this study was funded by a grant from the Japan Cardiovascular Research Foundation and supported by the Japanese Society of Hypertension **Declarations of potential conflicts of interest:** all of the study authors report receiving lecture fees from various pharmaceutical companies in Japan, including Novartis Pharma Japan (maker of valsartan - the first medication introduced) **Other:** unclear how the funding agencies are themselves funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of target BP levels, i.e., SBP of <140mmHg (L group) or ≥140mmHg and <150 mmHg (M group), will be performed with a minimization method based on the following assignment factors using a computer program: Sex: male or female; Age: younger than 75 years or 75 years or older; Seated SBP: less than 175 mmHg or 175 mmHg or higher; Antihypertensive therapy: not being treated or being treated; and Institution."
Allocation concealment (selection bias)	Unclear risk	“the patients were randomly assigned by the VALISH Data Center according to the following factors...”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and clinicians were not blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“End points and adverse events were blindly evaluated according to the prospective, randomised, open-label, blinded end point design by the end-point committee and the safety committee, respectively.”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More participants (181 = 5.9%) withdrew or were lost to follow-up than experienced the primary outcome. This included 82/1627 assigned to the lower (< 140 mmHg) BP target and 99/1633 assigned to the higher target. No sensitivity analysis was performed
Selective reporting (reporting bias)	Low risk	Reporting appears complete
Other bias	Unclear risk	How participants were selected for the per-protocol analysis was neither described in the main publication of findings (VALISH 2010), nor pre-defined in the preceding Rationale and Design publication which stated that the per-protocol analysis would exclude participants "...according to judging a criteria drawn up by the Statistical Committee of this study".

Wei 2013

Methods	PROBE study. Unclear if single site or multicenter 363 lower and 361 higher participants randomised and analysed by ITT
Participants	Chinese general practice outpatients > 70 years with either SBP ≥ 150 mm Hg and/or diastolic BP ≥ 90 mm Hg or a diagnosis of hypertension and current antihypertensive medication **Exclusions**: secondary hypertension, valvular heart disease, chronic kidney dysfunction (serum creatinine ≥ 3.0 mg/dL), previous myocardial infarction or stroke in the preceding 6 months, NYHA ≥ class III CHF, echocardiography determining left ventricular ejection fraction < 40%, hepatic dysfunction, autoimmune disorders, malignant tumour, Alzheimer's disease, and "other noncardiovascular diseases potentially causing death before the end of the study". Mean age: 76.5 years. Baseline BP 160/84. 66% men, 23% had diabetes, 25% smoked
Interventions	Lower BP target of < 140/90 versus higher BP target of < 150/90. Participants were started with single-drug treatment of an ACE inhibitor (benzene enalapril 10 mg/d), a beta -blocker (bisoprolol 2.5–5 mg or metoprolol 50–100 mg/d), a CCB (amlodipine 5–10 mg/d), or a diuretic (indapamide 1.5–2.5 mg/d). Presumably initial choice of therapeutic was up to the treating physician (not stated). It is unclear whether, or how, participants already treated at baseline were switched to study medications. To achieve the target BP, 1, 2, or 3 additional antihypertensive drugs could be added stepwise. If quadruple antihypertensive therapy (CCB + beta -blocker + ACE inhibitor + diuretic) failed to achieve the BP goal increasing the dose of antihypertensive drugs was recommended. BP was measured at 4 weeks, 3 months, 6 months, and every 6 months thereafter. Achieved BP at study completion 135.7/76.2 (lower) versus 149.7/82.1 (higher)
Outcomes	The primary outcome was the combined incidence of fatal/nonfatal stroke, acute myocardial infarction, and other cardiovascular deaths (sudden death and heart failure death). Secondary endpoints were deaths from any causes.
Notes	**Dates:** not reported. Mean follow-up 4 years **Funding Source:** not reported **Declarations of Interest:** not reported **Other:** an abstract was published in 2011 (first author Jin, Wei 2013) with a completed analysis and no mention of Wei (the lead author of the final publication) as a co-investigator. E-mail queries to co-authors confirm that first author Wei was a late addition to the project.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomly assigned to either intensive antihypertensive treatment or standard treatment by using a computer-generated table of random numbers."
Allocation concealment (selection bias)	Unclear risk	Method of allocation not reported
Blinding of participants and personnel (performance bias)	High risk	Participants and clinicians were not blinded

Wei 2013 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"In order to reduce investigation bias, endpoints were evaluated by the members of the Endpoint Evaluation Committee, who were blinded to the treatment assignments and the time course of BP."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lower BP target: 2 discontinued treatment, 1 withdrew consent, 1 lost to follow-up (1.1%) Higher BP target: 7 discontinued treatment, 5 withdrew consent, 2 lost to follow-up (3.9%) Although an ITT analysis was stated it is unclear how missing data was handled.
Selective reporting (reporting bias)	Low risk	Reported adverse events selectively only. Total serious adverse events not provided.
Other bias	High risk	An initial analysis of this study was published in abstract form with no mention of Wei (the lead author of the final publication) as a co-investigator. E-mail queries to co-authors confirm that first author Wei was a late addition to the project.

ACE: angiotensin-converting enzyme; **BP**: blood pressure; **CCB**: calcium channel blocker; **CHF**: congestive heart failure; **ITT**: intention-to-treat; **MI**: myocardial infarction; **NYHA**: New York Heart Association; **PROBE**: Prospective Randomised Open Blinded End-point assessment

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

Study	Reason for exclusion
Arima 2006	Participants were not randomised to different BP targets
Denardo 2010	Participants were not randomised to different BP targets
Ihle-Hansen 2015	Examined the data according to achieved BP but did not randomise to different BP targets (participants were instead randomised to intense treatment of all risk factors including systolic BP < 140 versus usual care by GP)
Ogihara 2008	Participants were not randomised to different BP targets
Ogihara 2009	Participants were not randomised to different BP targets
Ogihara 2011	Participants were not randomised to different BP targets
Ogihara 2012	Participants were not randomised to different BP targets
Omboni 2015	Participants were not randomised to different BP targets
Saito 2011	Participants were not randomised to different BP targets
Saxby 2008	Participants were not randomised to different BP targets
SPRINT 2015	Although an older adult subgroup was reported, subjects in this RCT were randomised to lower BP targets than considered in this review (< 120 vs < 140 mmHg systolic)
Steurer 2016	Compared lower BP targets than considered in this review (< 120 vs < 140 mmHg systolic)

Study	Reason for exclusion
Zhang 2011	Participants were not randomised to different BP targets

BP: blood pressure; **GP**: general practitioner; **SBP**: systolic blood pressure

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

Cai 2017

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Trial registry only. Study is recruiting. May qualify for inclusion once complete (compares SBP 110-130 mmHg to SBP 130-150 mmHg). Estimated completion Dec 2021

White 2013

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	Published protocol only. Recrutiment completed. Final data collection anticipated Sept 2018. Randomises to 24-h SBP < 130 versus 24-h SBP < 145. Does not appear to be examining cardiovascular outcomes (focuses on cognition and mobility)

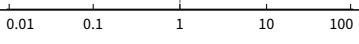
DATA AND ANALYSES

Comparison 1. Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.99, 1.54]
2 Stroke	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.94, 1.67]
3 Cardiovascular serious adverse events	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.98, 1.45]
4 Cardiovascular mortality	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.06, 2.19]
5 Non-cardiovascular mortality	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.46]
6 Unplanned hospitalisation	1	3079	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.55, 2.53]
7 Cardiovascular serious adverse events (by component)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Cerebrovascular disease	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.93, 1.61]
7.2 Cardiac disease	3	8221	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.82, 1.79]
7.3 Vascular disease	1	4418	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.94]
7.4 Renal failure	2	7497	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.89]
8 Total serious adverse events	1	3079	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.24]
9 Total minor adverse events	2	7497	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]
10 Withdrawals due to adverse effects	2	7497	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.19]
11 Mean systolic BP achieved	3	8221	Mean Difference (IV, Fixed, 95% CI)	8.88 [8.38, 9.39]
12 Mean diastolic BP achieved	3	8221	Mean Difference (IV, Fixed, 95% CI)	3.09 [2.72, 3.47]

Analysis 1.1. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 1 All-cause mortality.

Study or subgroup	Higher BP target n/N	Lower BP target n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
JATOS 2008	42/2206	54/2212		41.9%	0.78[0.52,1.16]
VALISH 2010	30/1534	24/1545		18.58%	1.26[0.74,2.14]
Wei 2013	87/361	51/363		39.52%	1.72[1.25,2.35]
Total (95% CI)	**4101**	**4120**		**100%**	**1.24[0.99,1.54]**
Total events: 159 (Higher BP target), 129 (Lower BP target)					
Heterogeneity: Tau²=0; Chi²=9.32, df=2(P=0.01); I²=78.53%					



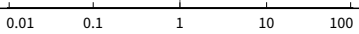
Favours higher BP target — Favours lower BP target

Study or subgroup	Higher BP target n/N	Lower BP target n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.9(P=0.06)					

Favours higher BP target | Favours lower BP target

Analysis 1.2. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 2 Stroke.

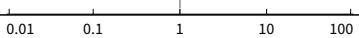
Study or subgroup	Higher BP target n/N	Lower BP target n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
JATOS 2008	42/2206	44/2212		54.36%	0.96[0.63,1.45]
VALISH 2010	23/1534	16/1545		19.73%	1.45[0.77,2.73]
Wei 2013	36/361	21/363		25.91%	1.72[1.03,2.89]
Total (95% CI)	**4101**	**4120**		**100%**	**1.25[0.94,1.67]**
Total events: 101 (Higher BP target), 81 (Lower BP target)					
Heterogeneity: Tau^2=0; Chi^2=3.25, df=2(P=0.2); I^2=38.38%					
Test for overall effect: Z=1.54(P=0.12)					



Favours higher BP target | Favours lower BP target

Analysis 1.3. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 3 Cardiovascular serious adverse events.

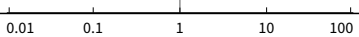
Study or subgroup	Higher BP target n/N	Lower BP target n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
JATOS 2008	86/2206	86/2212		49.76%	1[0.75,1.34]
VALISH 2010	52/1534	47/1545		27.13%	1.11[0.76,1.64]
Wei 2013	67/361	40/363		23.11%	1.68[1.17,2.42]
Total (95% CI)	**4101**	**4120**		**100%**	**1.19[0.98,1.45]**
Total events: 205 (Higher BP target), 173 (Lower BP target)					
Heterogeneity: Tau^2=0; Chi^2=4.93, df=2(P=0.09); I^2=59.43%					
Test for overall effect: Z=1.75(P=0.08)					



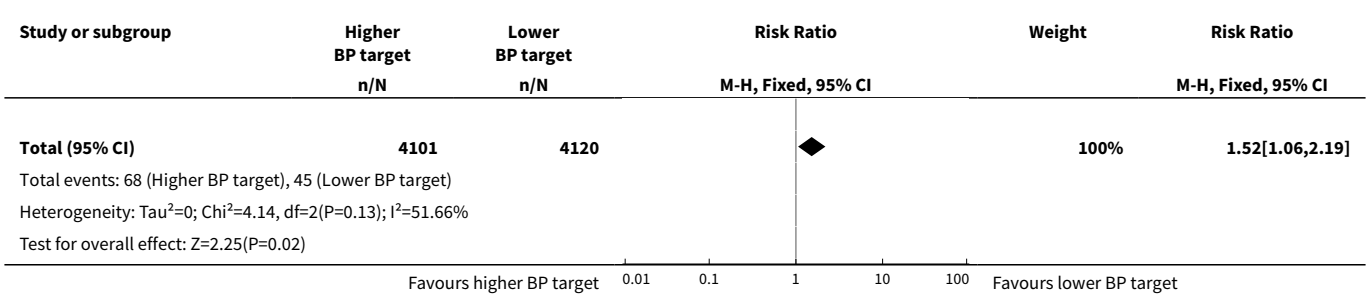
Favours higher BP target | Favours lower BP target

Analysis 1.4. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 4 Cardiovascular mortality.

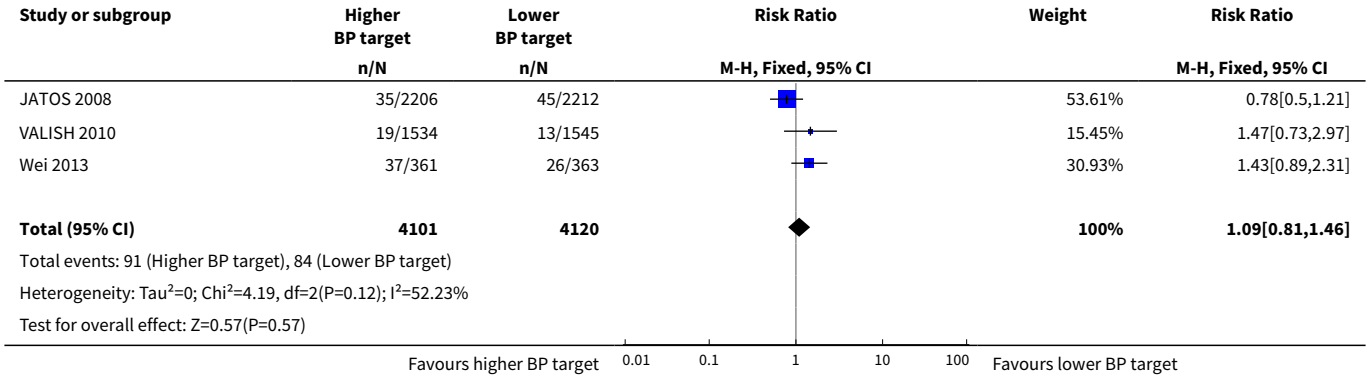
Study or subgroup	Higher BP target n/N	Lower BP target n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
JATOS 2008	7/2206	9/2212		20.03%	0.78[0.29,2.09]
VALISH 2010	11/1534	11/1545		24.42%	1.01[0.44,2.32]
Wei 2013	50/361	25/363		55.55%	2.01[1.27,3.18]



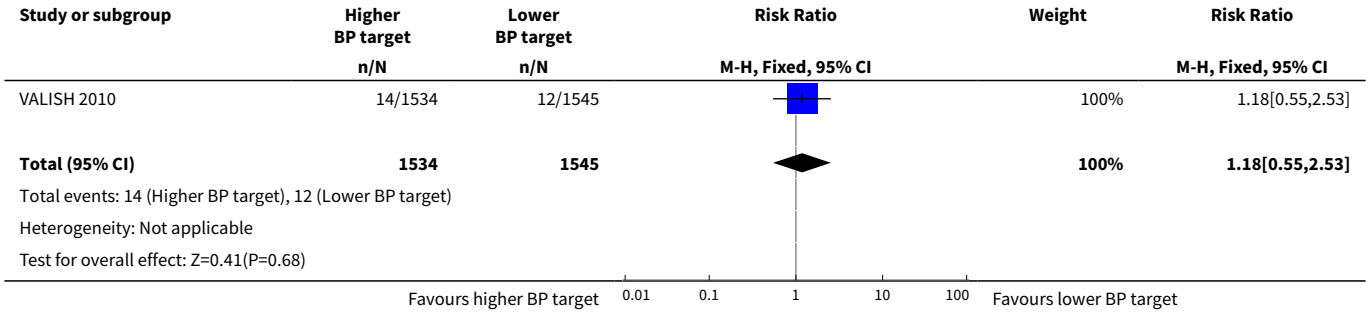
Favours higher BP target | Favours lower BP target



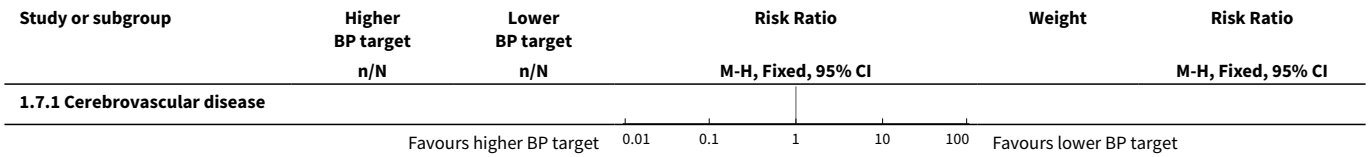
Analysis 1.5. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 5 Non-cardiovascular mortality.

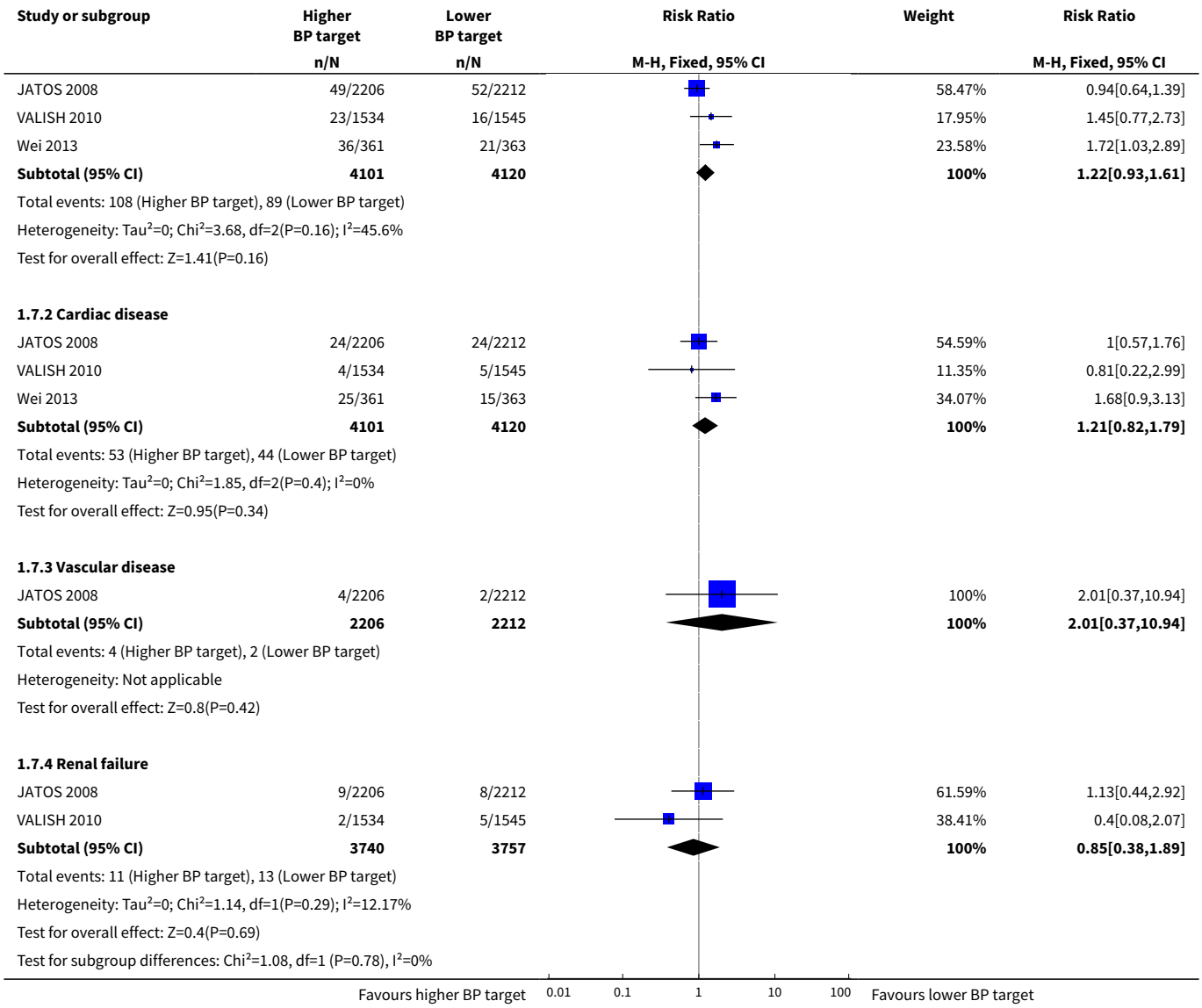


Analysis 1.6. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 6 Unplanned hospitalisation.

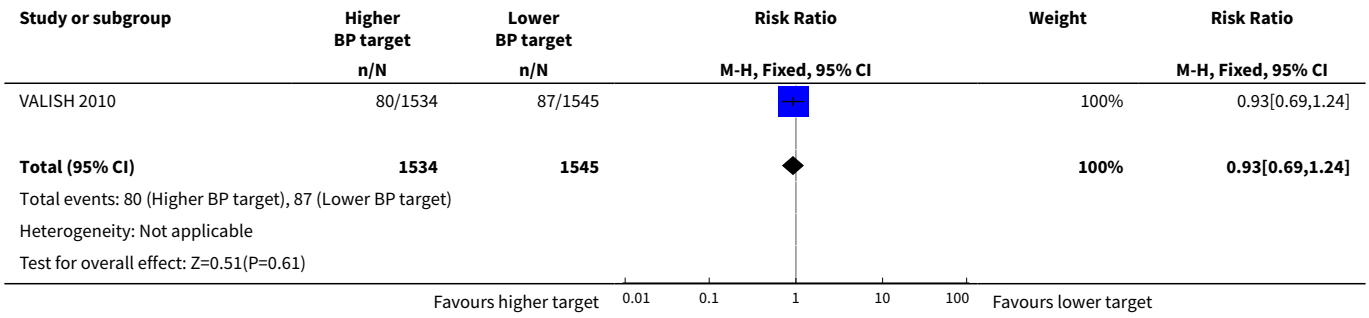


Analysis 1.7. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 7 Cardiovascular serious adverse events (by component).

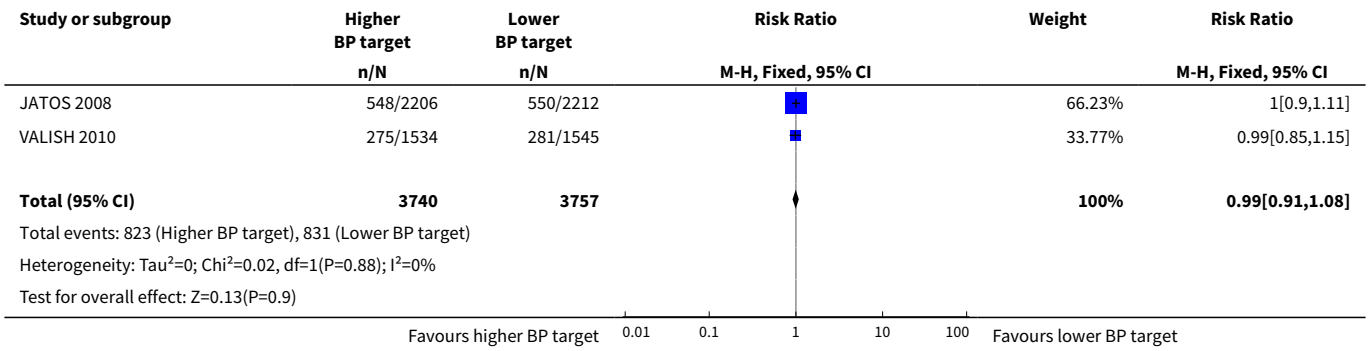




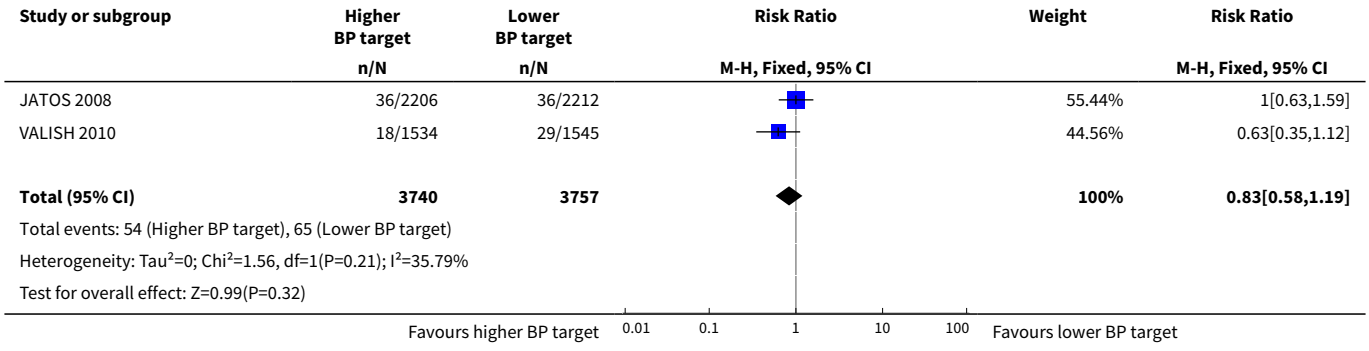
Analysis 1.8. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 8 Total serious adverse events.



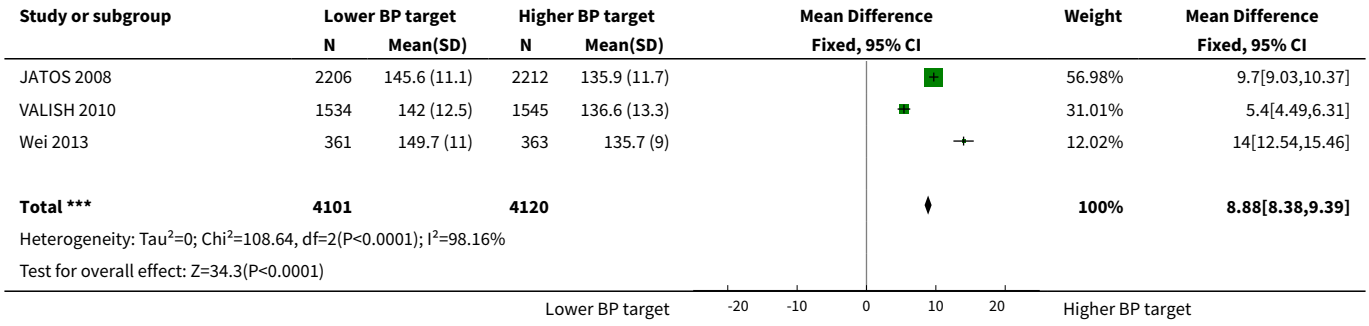
Analysis 1.9. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 9 Total minor adverse events.



Analysis 1.10. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 10 Withdrawals due to adverse effects.



Analysis 1.11. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 11 Mean systolic BP achieved.



Analysis 1.12. Comparison 1 Higher (< 150-160/95-100 mmHg) versus lower (< 140/90 mmHg) BP target, Outcome 12 Mean diastolic BP achieved.

Study or subgroup	Higher BP target N	Higher BP target Mean(SD)	Lower BP target N	Lower BP target Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
JATOS 2008	2206	78.1 (8.9)	2212	74.8 (9.1)		49.88%	3.3[2.77,3.83]
VALISH 2010	1534	76.5 (8.9)	1545	74.8 (8.8)		35.95%	1.7[1.07,2.33]
Wei 2013	361	82.1 (7.5)	363	76.2 (6.1)		14.16%	5.9[4.9,6.9]
Total ***	**4101**		**4120**			**100%**	**3.09[2.72,3.47]**
Heterogeneity: Tau²=0; Chi²=50.15, df=2(P<0.0001); I²=96.01%							
Test for overall effect: Z=16.17(P<0.0001)							

APPENDICES

Appendix 1. Search strategies

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies (CRS-Web)
Search Date: 3 February 2017

#1 MeSH DESCRIPTOR Aged EXPLODE ALL TREES

#2 MeSH DESCRIPTOR Health Services for the Aged

#3 MeSH DESCRIPTOR Homes for the Aged

#4 MeSH DESCRIPTOR Long-term Care

#5 MeSH DESCRIPTOR Nursing Care

#6 MeSH DESCRIPTOR Nursing Homes EXPLODE ALL TREES

#7 ((“advanced years” or ageing or aging or elder* or elderly or frail or geriatric* or gerontolog* or “later life” or “nursing care” or nursing home* or “old age” or “oldest old” or pensioner* or post-menopausal or postmenopausal or senior or seniors))

#8 (old* NEAR3 (adult* or female* or male* or men or people or person or women))

#9 ((65 year* or "over 65" or "over 70" or "over 75" or "over 80" or "over 85" or 85 year*))

#10 ((aged or aging or ageing or elder* or geriatric* or gerontolog*)):SO

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 ((goal* or intensive* or strict* or target* or tight*) NEAR5 (antihypertensive* anti-hypertensive* or bp or control or dbp or diastolic or pressure* or sbp or systolic or treat*))

#13 MeSH DESCRIPTOR Antihypertensive Agents EXPLODE ALL TREES

#14 (ceiling diuretic* OR loop diuretic*)

#15 ((amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*))

#16 ((chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide))

#17 (sodium chloride symporter inhibitor* or sodium potassium chloride symporter inhibitor*)

#18 #14 OR #15 OR #16 OR #17

#19 (angiotensin converting enzyme inhibit*)

#20 (ace NEAR2 inhibit*)

#21 acei

#22 ((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))

#23 #19 OR #20 OR #21 OR #22

#24 (angiotensin NEAR3 (receptor antagon* or receptor block*))

#25 (arb or arbs)

#26 ((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))

#27 #24 OR #25 OR #26

#28 ((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))

#29 (calcium NEAR2 (antagonist* or block* or inhibit*))

#30 #28 OR #29

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

#32 ((reserpine or serpentina or rauwolfia or serpasil))

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

#34 ((hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat))

#35 #31 OR #32 OR #33 OR #34

#36 ((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))

#37 (beta NEAR2 (adrenergic or antagonist* or block* or receptor*))

#38 #36 OR #37

#39 ((alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin))

#40 (adrenergic NEAR2 (alpha or antagonist*))

#41 ((adrenergic or alpha or receptor*) NEAR2 block*)

#42 #39 OR #40 OR #41

#43 #13 OR #18 OR #23 OR #27 OR #30 OR #35 OR #38 OR #42

#44 RCT:DE

#45 (Review OR Meta-Analysis):MISC2

#46 #44 OR #45

#47 #11 AND #12 AND #43 AND #46 (129)

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Database: Cochrane Central Register of Controlled Trials on Wiley <2017, Issue 2> via Cochrane Register of Studies (CRS-Web)
Search Date: 3 February 2017

#1 MeSH DESCRIPTOR Aged EXPLODE ALL TREES AND CENTRAL:TARGET
#2 MeSH DESCRIPTOR Health Services for the Aged AND CENTRAL:TARGET
#3 MeSH DESCRIPTOR Homes for the Aged AND CENTRAL:TARGET
#4 MeSH DESCRIPTOR Long-term Care AND CENTRAL:TARGET
#5 MeSH DESCRIPTOR Nursing Care AND CENTRAL:TARGET

#6 MeSH DESCRIPTOR Nursing Homes EXPLODE ALL TREES AND CENTRAL:TARGET

#7 ((“advanced years” or ageing or aging or elder* or elderly or frail or geriatric* or gerontolog* or “later life” or “nursing care” or nursing home* or “old age” or “oldest old” or pensioner* or post-menopausal or postmenopausal or senior or seniors)) AND CENTRAL:TARGET

#8 (old* NEAR3 (adult* or female* or male* or men or people or person or women)) AND CENTRAL:TARGET

#9 ((65 year* or "over 65" or "over 70" or "over 75" or "over 80" or "over 85" or 85 year*)) AND CENTRAL:TARGET

#10 ((aged or aging or ageing or elder* or geriatric* or gerontolog*)):SO AND CENTRAL:TARGET

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND CENTRAL:TARGET

#12 ((goal* or intensive* or strict* or target* or tight*) NEAR5 (antihypertensive* anti-hypertensive* or bp or control or dbp or diastolic or pressure* or sbp or systolic or treat*)) AND CENTRAL:TARGET

#13 MeSH DESCRIPTOR Antihypertensive Agents EXPLODE ALL TREES AND CENTRAL:TARGET

#14 (ceiling diuretic* OR loop diuretic*) AND CENTRAL:TARGET

#15 ((amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)) AND CENTRAL:TARGET

#16 ((chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide)) AND CENTRAL:TARGET

#17 (sodium chloride symporter inhibitor* or sodium potassium chloride symporter inhibitor*) AND CENTRAL:TARGET

#18 #14 OR #15 OR #16 OR #17 AND CENTRAL:TARGET

#19 (angiotensin converting enzyme inhibit*) AND CENTRAL:TARGET

#20 (ace NEAR2 inhibit*) AND CENTRAL:TARGET

#21 acei AND CENTRAL:TARGET

#22 ((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)) AND CENTRAL:TARGET

#23 #19 OR #20 OR #21 OR #22 AND CENTRAL:TARGET

#24 (angiotensin NEAR3 (receptor antagon* or receptor block*)) AND CENTRAL:TARGET

#25 (arb or arbs) AND CENTRAL:TARGET

#26 ((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)) AND CENTRAL:TARGET

#27 #24 OR #25 OR #26 AND CENTRAL:TARGET

#28 ((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)) AND CENTRAL:TARGET

#29 (calcium NEAR2 (antagonist* or block* or inhibit*)) AND CENTRAL:TARGET

#30 #28 OR #29 AND CENTRAL:TARGET

#31 ((methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or "methyl dopa" or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or "alpha methyl dopa")) AND CENTRAL:TARGET

#32 ((reserpine or serpentina or rauwolfia or serpasil)) AND CENTRAL:TARGET

#33 ((clonidine or adesipress or arkamin or caprysin or catapres* or catasan or chlofazolin or chlophazolin or clinidine or clofelin* or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin* or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or "st 155" or "tesno timelets")) AND CENTRAL:TARGET

#34 ((hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat)) AND CENTRAL:TARGET

#35 #31 OR #32 OR #33 OR #34 AND CENTRAL:TARGET

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

#37 (beta NEAR2 (adrenergic or antagonist* or block* or receptor*)) AND CENTRAL:TARGET

#38 #36 OR #37 AND CENTRAL:TARGET

#39 ((alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin)) AND CENTRAL:TARGET

#40 (adrenergic NEAR2 (alpha or antagonist*)) AND CENTRAL:TARGET

#41 ((adrenergic or alpha or receptor*) NEAR2 block*) AND CENTRAL:TARGET

#42 #39 OR #40 OR #41 AND CENTRAL:TARGET

#43 #13 OR #18 OR #23 OR #27 OR #30 OR #35 OR #38 OR #42 AND CENTRAL:TARGET

#44 #11 AND #12 AND #43 (169)

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Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 3 February 2017
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1 exp aged/ (2656661)

2 health services for the aged/ or homes for the aged/ or long-term care/ or nursing care/ or exp nursing homes/ (99860)

3 (advanced years or ageing or aging or elder? or elderly or frail or geriatric? or gerontolog$ or later life or nursing care or nursing home? or old age or oldest old or pensioner? or post-menopausal or postmenopausal or senior or seniors).tw. (467132)

4 (old$ adj3 (adult? or female? or male? or men or people or person or women)).tw. (223842)

5 ("65 year$" or "over 65" or "over 70" or "over 75" or "over 80" or "over 85" or "85 year$").tw. (87262)

6 (aged or aging or ageing or elder$ or geriatric$ or gerontolog$).jw,nw. (123914)

7 or/1-6 (3058954)

8 ((goal? or intensive$ or strict$ or target$ or tight$) adj5 (antihypertensive? anti-hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat$)).tw. (113185)

9 exp antihypertensive agents/ (240187)

10 exp thiazides/ (14950)

11 exp sodium chloride symporter inhibitors/ (13762)

12 exp sodium potassium chloride symporter inhibitors/ (13118)

13 ((ceiling or loop) adj diuretic?).tw. (2368)

14 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (31754)

15 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (2185)

16 or/10-15 [THZ] (46629)

17 exp angiotensin-converting enzyme inhibitors/ (40812)

18 angiotensin converting enzyme inhibit$.tw. (17081)

19 (ace adj2 inhibit$).tw. (17161)

20 acei.tw. (2685)

21 (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. (24880)

22 or/17-21 [ACEI] (55316)

23 exp Angiotensin Receptor Antagonists/ (20230)

24 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (11042)

25 arb?.tw. (4815)

26 (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. (14453)

27 or/23-26 [ARB] (28524)

28 exp calcium channel blockers/ (77014)

29 (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. (57697)

30 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (35853)

31 or/28-30 [CCB] (102777)

32 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (14955)

33 (reserpine or serpentina or rauwolfia or serpasil).mp. (19775)

34 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (18801)

35 exp hydralazine/ (4569)

36 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (4222)

37 or/32-36 [CNS] (56145)

38 exp adrenergic beta-antagonists/ (79891)

39 (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. (58765)

40 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (91362)

41 or/38-40 [BB] (146852)

42 exp adrenergic alpha antagonists/ (48281)

43 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (13197)

44 (adrenergic adj2 (alpha or antagonist?)).tw. (18811)

45 ((adrenergic or alpha or receptor?) adj2 block$).tw. (53474)

46 or/42-45 [AB] (107263)

47 hypertension/ (214045)

48 hypertens$.tw. (338051)

49 ((high or elevat$ or rais$) adj2 blood pressure).tw. (23720)

50 or/47-49 (398358)

51 randomized controlled trial.pt. (446305)

52 controlled clinical trial.pt. (91768)

53 randomized.ab. (339401)

54 placebo.ab. (167835)

55 clinical trials as topic/ (180932)

56 randomly.ab. (234159)

57 trial.ti. (151570)

58 or/51-57 (1002859)

59 animals/ not (humans/ and animals/) (4278833)

60 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (844365)

61 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti. (13602)

62 58 not (59 or 60 or 61) (884239)

63 7 and 8 and (9 or 16 or 22 or 27 or 31 or 37 or 41 or 46) and 50 and 62 (1012)

64 remove duplicates from 63 (956)

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Database: Embase <1974 to 2017 February 2>
Search Date: 3 February 2017
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1 exp aged/ (2583775)

2 exp elderly care/ (71836)

3 home for the aged/ (11287)

4 exp long term care/ (1451228)

5 exp nursing care/ (37779)

6 nursing home/ (50235)

7 (advanced years or ageing or aging or elder? or elderly or frail or geriatric? or gerontolog$ or later life or nursing care or nursing home? or old age or oldest old or pensioner? or post-menopausal or postmenopausal or senior or seniors).tw. (688198)

8 (old$ adj3 (adult? or female? or male? or men or people or person or women)).tw. (381010)

9 ("65 year$" or "over 65" or "over 70" or "over 75" or "over 80" or "over 85" or "85 year$").tw. (148322)

10 (aged or aging or ageing or elder$ or geriatric$ or gerontolog$).jw. (166512)

11 or/1-10 (4311485)

12 ((goal? or intensive$ or strict$ or target$ or tight$) adj5 (antihypertensive? anti-hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat$)).tw. (192761)

13 exp antihypertensive agent/ (646863)

14 exp thiazide diuretic agent/ (51733)

15 exp loop diuretic agent/ (65914)

16 ((loop or ceiling) adj diuretic?).tw. (3860)

17 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (41553)

18 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (3689)

19 or/14-18 [THZ] (119990)

20 exp dipeptidyl carboxypeptidase inhibitor/ (157164)

21 angiotensin converting enzyme inhibit$.tw. (22649)

22 (ace adj2 inhibit$).tw. (26678)

23 acei.tw. (5866)

24 (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. (35656)

25 or/20-24 [ACEI] (164652)

26 exp angiotensin receptor antagonist/ (76543)

27 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (17451)

28 arb?.tw. (10619)

29 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw. (24392)

30 or/26-29 [ARB] (82203)

31 calcium channel blocking agent/ (56975)

32 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (78076)

33 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (46937)

34 or/31-33 [CCB] (139564)

35 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (28824)

36 (reserpine or serpentina or rauwolfia or serpasil).mp. (29009)

37 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (45476)

38 hydralazine/ (18128)

39 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (6289)

40 or/35-39 [CNS] (106640)

41 exp beta adrenergic receptor blocking agent/ (269491)

42 (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. (79478)

43 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (116165)

44 or/41-43 [BB] (323332)

45 exp alpha adrenergic receptor blocking agent/ (130812)

46 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (16623)

47 (adrenergic adj2 (alpha or antagonist?)).tw. (18188)

48 ((adrenergic or alpha or receptor?) adj2 block$).tw. (71187)

49 or/45-48 [AB] (197816)

50 exp hypertension/ (631543)

51 (hypertens$ or antihypertens$).tw. (546297)

52 ((high or elevat$ or rais$) adj2 blood pressure).tw. (35424)

53 or/50-52 (799059)

54 double blind$.mp. (218883)

55 placebo$.tw. (253070)

56 blind$.tw. (340091)

57 or/54-56 (492194)

58 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5883553)

59 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (700427)

60 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti. (19965)

61 57 not (58 or 59 or 60) (457458)

62 11 and 12 and (13 or 19 or 25 or 30 or 34 or 40 or 44 or 49) and 53 and 61 (617)

63 remove duplicates from 62 (601)

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Database: ClinicalTrials.gov
Search Date: 3 February 2017

Search terms: (intensive OR strict OR target OR tight) AND (randomized) AND (aged OR elderly OR geriatric OR older)
Study type: Interventional Studies
Conditions: hypertension
Outcome measure: blood pressure (34)

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Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 3 February 2017
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hypertens* AND aged AND intensive
hypertens* AND aged AND strict
hypertens* AND aged AND target*
hypertens* AND aged AND tight

hypertens* AND elderly AND intensive
hypertens* AND elderly AND strict
hypertens* AND elderly AND target*
hypertens* AND elderly AND tight

hypertens* AND older AND intensive
hypertens* AND older AND strict
hypertens* AND older AND target*
hypertens* AND older AND tight

hypertens* AND geriatric AND intensive
hypertens* AND geriatric AND strict
hypertens* AND geriatric AND target*
hypertens* AND geriatric AND tight

CONTRIBUTIONS OF AUTHORS

Dr Garrison drafted both the protocol and the full review and is the guarantor of the review. All authors performed critical review and approved the final text. Drs Garrison, McCracken, Korownyk and Allan searched for and identified studies for inclusion. Drs Korownyk and Kolber assessed studies for bias and extracted data. Dr Heran entered data and studies into Review Manager 5 and performed the analyses. Dr Allan verified the data extraction and entry into Review Manager 5.

DECLARATIONS OF INTEREST

Scott Garrison: none

Mike Kolber: none

Tina Korownyk: none

Rita McCracken: none

Benji Heran: none

G Michael Allan: none

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Internal sources

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  Clinical practice income (RKM)

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- Providence Health Care Research Award, Canada.

  Competitive research award from the author's local health authority (RKM)
- British Columbia College of Family Physicians Research Award, Canada.

  Competitive research award from professional body (RKM)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol we stated that we would examine outcomes at two years and, if some studies did not extend that far, at one year. Only one of our studies reported two-year outcomes. Rather than interpolating results from these other studies to the two-year time frame, we chose instead to report outcomes using the mean period of observation from each analysis (ranging from 2.4 to 2.6 years). We made this revision upon recognizing it to be the standard approach in other Cochrane Reviews.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Blood Pressure [*drug effects]; Blood Pressure Determination; Cardiovascular Diseases [epidemiology]; Cause of Death; Hospitalization [statistics & numerical data]; Hypertension [*drug therapy] [mortality]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Reference Values; Stroke [epidemiology]; Systole

MeSH check words

Aged; Female; Humans; Male