National Institute for Health and Care Excellence

Final

Hypertension in adults (update)

[J] Evidence review for blood pressure targets

NICE guideline NG136

Evidence review underpinning recommendation 1.4.23

March 2022

Final

This evidence review was developed by the National Guideline Centre

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Contents

1 Blood pressure targets

1.1 Review question

What are the optimum blood pressure targets for adults with diagnosed primary hypertension and established cardiovascular disease?

1.1.1 Introduction

It is well-established that the cardiovascular disease (CVD) risks associated with hypertension continue to increase as blood pressure rises. Therefore, once a diagnosis of arterial hypertension has been secured (and any relevant cause identified and treated), the aim of intervention is to reduce blood pressure to a level at which the risk of cardiovascular events is minimised without unduly increasing the deleterious consequences of anti-hypertensive drug treatment.

As described in the 2019 NICE guideline NG136 (Hypertension in adults: diagnosis and management), a clinic blood pressure target of less than 140/90 mmHg (average waking home or ambulatory blood pressure less than 135/85 mmHg) was identified as appropriate for most hypertensive individuals, with a slightly higher threshold (office less than 150/90 mmHg, average waking home or ambulatory less than 145/85 mmHg) for those aged 80 years or more. However, these recommendations were not developed specifically for individuals with a diagnosis of both hypertension and CVD. Given that people with established CVD have an intrinsically higher risk of CVD events (compared to a non-CVD population) then it is entirely plausible that further reduction in blood pressure beyond those recommended in NG136 might confer a level of benefit which exceeds any associated adverse effects.

This chapter therefore reviews the evidence for this population in order to identify the optimum blood pressure target for people with a confirmed diagnosis of both arterial hypertension and CVD.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (over 18 years) with diagnosed primary hypertension and established cardiovascular disease. • Stratify by age <80 years and age ≥80 years

Intervention: lower/intensive blood pressure treatment target	**Blood pressure targets for those aged <80 years**
	• Systolic blood pressure target:
	  ○ clinic measurement 130 mmHg or less;
	  ○ home, ambulatory or unattended/automated clinic measurement 125 or less.
	And/or:
	• Diastolic blood pressure target:
	  ○ clinic measurement 80 mmHg or less
	  ○ home, ambulatory or unattended/automated clinic measurement 75 mmHg or less.
	
	Blood pressure targets for those aged ≥80 years
	• Systolic blood pressure target:
	  ○ clinic measurement below 140 mmHg

	○ home, ambulatory or unattended/automated clinic measurement below 135 mmHg. And/or: • Diastolic blood pressure target: ○ clinic measurement below 80 mmHg ○ home, ambulatory or unattended/automated clinic measurement below 75 mmHg.
Comparison: standard blood pressure treatment target	**Blood pressure targets for those aged <80 years** • Systolic blood pressure target: ○ clinic measurement 140 mmHg or less; ○ home, ambulatory or unattended/automated clinic measurement 135 or less. And/or: • Diastolic blood pressure target: ○ clinic measurement 90 mmHg or less ○ home, ambulatory or unattended/automated clinic measurement 85 mmHg or less. **Blood pressure targets for those aged ≥80 years** • Systolic blood pressure target: ○ clinic measurement below 150 mmHg ○ home, ambulatory or unattended/automated clinic measurement below 145 mmHg. And/or: • Diastolic blood pressure target: ○ clinic measurement below 90 mmHg ○ home, ambulatory or unattended/automated clinic measurement below 85 mmHg.
Outcomes	• All-cause mortality • Health-related quality of life • Stroke (ischaemic or primary cerebral haemorrhage) • Acute coronary syndrome (e.g. myocardial infarction, unstable angina) • Heart failure needing hospitalisation • Vascular procedures (including lower limb revascularisation, coronary and carotid artery procedures) • Discontinuation or dose reduction due to side effects • Resource use (e.g. number of pills, GP visits for BP checks, referral to specialist clinics, emergency admissions) • Side effect 1: Acute kidney injury • Side effect 2: Deterioration in estimated glomerular filtration rate (eGFR) >30% • Side effect 3: Injurious falls • [Combined cardiovascular disease event outcomes in the absence of MI and stroke data] • [Coronary heart disease event outcome in the absence of MI data]
Study design	• RCTs, subgroup analyses from RCTs and systematic reviews of RCTs • Published network meta-analyses and individual participant data meta-analyses

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

This review was undertaken to identify whether there is evidence to support different blood pressure targets in people with hypertension who also have cardiovascular disease, compared to those without cardiovascular disease. Therefore, the blood pressure target thresholds chosen for the standard blood pressure treatment group reflect the 2019 recommendation in NG136, as this defined current practice at the time of the review. The intervention group thresholds represent lower targets than the 2019 NICE recommendations. As the population is different from that in NG136, evidence from this update is not being combined with the review in that version of the guideline.

For the purposes of this review, established CVD includes past medical history of:

- ischaemic heart disease: acute coronary syndrome, for example, myocardial infarction, (silent or symptomatic), angina with confirmed underlying coronary artery disease, previous percutaneous coronary intervention, or previous coronary artery bypass graft surgery
- cerebrovascular disease: stroke and/or transient ischemic attack (TIA), or haemorrhage or radiological evidence of prior stroke
- peripheral vascular disease: symptomatic claudication and/or confirmed peripheral vascular disease on angiography or abnormal ankle-brachial pressure index (ABPI) (<0.9)
- aortic aneurysm
- heart failure.

The 2019 recommendations in NG136 were largely based on evidence from an earlier guideline (CG127, an update published in 2011), as new evidence added in NG136 was insufficient to suggest the use of lower targets for the general population of adults with hypertension.

Regarding methods for combining data, it was agreed that any blood pressure targets from different studies below the thresholds stated would be pooled as the intervention group (for example, clinic SBP target <130 mmHg would be pooled with clinic SBP target <120 mmHg) and that studies using clinic measurements would be pooled with studies using equivalent unattended/automated, home or ambulatory measurements as defined in the protocol. These variables would be explored as subgroup analyses if heterogeneity is found in the primary analyses. Similarly, studies specifying a lower systolic blood pressure as the target would be pooled with those specifying a lower diastolic blood pressure target because the aim is still to lower blood pressure more intensively.

Regarding methods of analysis, all-cause mortality, stroke and acute coronary syndrome were considered to be time-to-event outcomes and hazard ratios were extracted or calculated where possible. However, not all studies reported enough information to calculate hazard ratios for these outcomes. Therefore, both the dichotomous and time-to-event outcome data were reported, but the primary measure for decision-making was the dichotomous data. This is because there was very little difference in the effect estimates from the hazard ratios and risk ratios, while the risk ratio analysis has the benefit of including all available data in a single pooled analysis for the outcome. Therefore, the hazard ratio outcomes have been included in the evidence summary but in greyed-out, italicised text to indicate that they were not the main analysis and to avoid double counting the data.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Seven trials reported in 15 papers were included in the review;[1, 5, 6, 8, 10, 11, 13, 15-17, 19, 20, 23-25]

these are summarised in Table 2 and Table 3 below. Evidence from these studies is presented in the clinical evidence summaries below (Table 4 and Table 5).

This included 1 published Cochrane review.[23] This was an individual participant data meta-analysis of the subgroup with existing cardiovascular disease from published trials comparing intensive versus standard blood pressure targets. This systematic review was incorporated with modifications and updated for this report as follows:

- The search was updated to identify trials published since the cut-off date in the Cochrane review.
- The search was supplemented for all years to include terms for transient ischaemic attack (TIA) and aortic aneurysm, which are included in the definition of cardiovascular disease for this guideline but were not included in the Cochrane review.
- Data for PAST BP and SPS3 trials were taken from the original publications rather than the Cochrane review. For PAST BP this was because those with prior TIA were excluded from the Cochrane analysis, but are relevant to our review protocol. For SPS3 the reason was that the 10% of participants who were not hypertensive at baseline were excluded from the Cochrane analysis, but our protocol allows a study to be included if >80% of the population match our criteria and it is preferable to include the full RCT where possible.
- Risk of bias was re-assessed per outcome.
- Only outcomes from the Cochrane review that are relevant to our protocol were included, and additional outcomes were added to those analysed in the Cochrane review where they were available from primary trial reports.

Two of the studies (ACCORD[8, 10, 11] and HOT[15, 16]) included only adults aged 80 years or less and were analysed separately according to the protocol stratification. The remaining 5 trials included mixed populations of adults both above and below 80 years of age.

Owing to a lack of directly applicable evidence, studies using blood pressure target thresholds similar to, but not matching the protocol definitions were included but downgraded for indirectness. The available comparisons, which were pooled for analysis, were as follows:

- 2 studies compared SBP target <120 mmHg with <140 mmHg (ACCORD[8, 10, 11], SPRINT[1, 24, 25])
- 1 study compared BP target <120/80 mmHg with <140/90 mmHg, or <130/80 mmHg for the ~30% of patients with diabetes, chronic kidney disease, or a history of MI (RESPECT[17])
- 1 study compared SBP target <125 mmHg with targets 130-140 mmHg (PRESERVE[20])
- 1 study compared SBP target <130mmHg or a target reduction of 10 mmHg if baseline SBP 125 - 140 mm Hg with SBP <140 mmHg (PAST BP[13, 19])
- 1 study compared SBP target <130 with 130-149 mmHg (SPS3[5, 6])
- 1 study compared DBP target ≤80 or 85 mmHg with ≤90 mmHg (HOT[15, 16]; data available for CVD subgroup from Cochrane review pooled the ≤80 and 85 mmHg target groups as the intervention[23]).

All of the included trials used office blood pressure measurements, although in 1 study participants were also given home blood pressure monitors and it was unclear how often these reading may have informed the treat-to-target management decision.[20]

Data on withdrawals due to adverse effects were included where available as a measure of the protocol outcome of discontinuation or dose reduction due to side effects.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

Four other Cochrane reviews were identified but not included in this review. Three did not provide subgroup data for those with established cardiovascular disease,[2, 3, 14] and 1 was a protocol for a review with a population not matching the guideline review definition (>20% with CKD requiring lower BP target).[12] See also the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Age stratum: <80 years				
ACCORD study group 2010[8, 10, 11] (outcome data from Saiz 2020[23]) USA and Canada	(n=772) Intervention: Systolic BP targets <120 mmHg (n=759) Comparator: Systolic BP targets <140 mmHg	Primary hypertension and type 2 diabetes (prespecified subgroup analysis of those with previous CVD). Aged 40-79 years (mean 62 (8) years) CVD diagnoses • 86% ischaemic heart disease • 20% stroke Systolic BP between 130 and 180 mmHg (mean 138/74 mmHg)	Data from Cochrane review At 4.7 years: • All-cause mortality (N events) • Cardiovascular events (N events) • Number of drugs at end of trial	Participants also randomised to either intensive or standard glycaemic control in a 2x2 factorial design. For standard BP group: up-titration if SBP >160 mm Hg at a single visit or >140 mm Hg at 2 consecutive visits; down-titration encouraged if SBP was <135 mm Hg on 2 visits or <130 mmHg at 1 visit. For intensive group participants: medication up-titration if SBP ≥120 mm Hg. BP measured using an automated device after 5 minutes rest with the participant seated in a chair (average of 3 measurements).
HOT study group 1998[15, 16] (outcome data from Saiz 2020[23]) Asia, the Americas, and Europe	(n=2168) Intervention: Diastolic BP targets ≤80 or 85 mmHg (n=1064) Comparator: Diastolic BP targets ≤90 mmHg	Primary hypertension with or without type 2 diabetes (post hoc subgroup analysis of those with previous CVD). Aged 50–80 years (mean 62 years) CVD diagnoses • 95% ischaemic heart disease • 7% stroke	Data from Cochrane review At 3.8 years: • All-cause mortality (N events) • Cardiovascular events (N events) • Number of drugs at end of trial	Participants also randomised to aspirin vs placebo Previous CVD status accounted for in randomisation but subgroup analysis not prespecified Blood pressures were measured with an oscillometric semiautomatic Device three times with the patient seated after they had had 5 min rest.

Study	Intervention and comparison	Population	Outcomes	Comments
		Required DBP ≥100 mmHg and ≤115 mmHg on 2 occasions, at least 1 week apart. Mean (SD) baseline BP 174/106 (15/3) mmHg	• Withdrawal due to adverse effects	Treatment algorithm followed to up-titrate dose and add agents. Down-titration not mentioned. Indirect comparison: DBP ≤80 or 85 mmHg pooled as intervention group in Cochrane review
Age stratum: mixed <80 and ≥80 years				
PAST BP study group 2016[13, 19] (some outcome data also from Saiz 2020[23]) UK	(n=266) Intervention: Systolic BP targets <130mmHg or a target reduction of 10 mm Hg if their baseline BP 125 - 140 mm Hg. (n=263) Comparator: Systolic BP targets <140 mmHg	Adults with prior stroke or TIA and SBP ≥125 mmHg, with or without diabetes Mean age 72 (9) years CVD diagnoses • 48% stroke • 52% TIA • 16% coronary heart disease • 4% peripheral vascular disease • 2% heart failure Mean (SD) baseline BP 143(14)/80(10) vs 142(13)/80(10) mmHg	At 12 months • All-cause mortality (N events) • Stroke (N events) • Myocardial infarction (N events) • Number of drugs at end of trial • Falls • GP and practice nurse visits • Risk of emergency admission Data from Cochrane review[23]) (excluded those with TIA) • Withdrawal due to adverse effects	Blood pressure was measured using a British Hypertension Society validated automated electronic monitor supplied and validated for the study. Blood pressure was measured in a standardised way by a practice nurse. The patient was seated for 5 minutes and then 6 measurements taken at minute intervals. The second and third measurements were averaged to give the reading. BP lowering treatment followed NICE guideline. No formal down-titration of treatment if blood pressure was below target Sample size calculation of 305 per arm needed, but only 266 and 263 assigned to each group. However, the authors stated that: “our trial was adequately powered, as the observed standard deviation in blood pressure was less than we had anticipated in our sample size calculation. This is reflected in the statistical

Study	Intervention and comparison	Population	Outcomes	Comments
				significance of the small difference in observed blood pressure between arms." Indirect population: not all hypertensive Indirect BP target threshold comparison
SPRINT study group 2015[1, 25] (outcome data from Saiz 2020[23] and Vlachopoulos 2019[24]) USA	(n=779) Intervention: Systolic BP targets <120mmHg (n=783) Comparator: Systolic BP targets <140 mmHg	Primary hypertension without type 2 diabetes (pre-specified subgroup analysis of those with previous CVD) Aged at least 50 years; Mean age 70 (9) years. 37% of participants were above the age of 75 CVD diagnoses • 100% ischaemic heart disease or peripheral vascular disease Mean standard deviation (SD) baseline BP 139/76 (16/12) vs 138/74 (16/12) mmHg	Data from Cochrane review[23] At 3.26 years: • All-cause mortality (N events) • Number of drugs at end of trial Data from primary report[24]: • All-cause mortality (HR) • Stroke (N events and HR) • Myocardial infarction (N events and HR) • Heart failure (N events and HR) • Acute kidney injury or acute renal failure (N events and HR) • Injurious fall (N events and HR)	Titration of medications to target is based on a mean of 3 office blood pressure measurements obtained in the seated position using an automated measurement device. Actual strategy for blood pressure measurement varied within SPRINT. In the full study cohort the majority of participants (n=4,082) were alone throughout measurement. 2,247 participants were never alone, 1,746 were alone for the rest period only, and 570 were alone for BP measurement only. Treat-to-target protocol down-titrated participants' medication if their blood pressure fell below the pre-specified target Trial stopped early for benefit Downgraded for indirectness due to methods of measuring blood pressure
SPS3 study group 2013[5, 6]	(n=1501) Intervention: Systolic BP targets <130mmHg	Normotensive (10%) or hypertensive (90%) adults aged 30 years or over with recent history of (within 180 days), symptomatic, MRI-confirmed lacunar stroke	At 3.7 years • All-cause mortality (N events and HR)	Participants also randomised to clopidogrel vs placebo.

Study	Intervention and comparison	Population	Outcomes	Comments
North America, Latin America, and Spain.	(n=1519) Comparator: Systolic BP targets 130-149mmHg	Mean age 63 (10.8) years CVD diagnoses • 99% stroke (1% TIA) • 11% ischaemic heart disease Mean (SD) baseline BP 142(19)/78(10) vs 144(9)/79(11) mmHg	• Stroke (N events and HR) • Myocardial infarction (N events and HR) • Number of drugs at end of trial	Blood pressure was measured three times at every visit and the average measurement was used to decide hypertensive status. All study sites were provided with automated Colin Press-Mate BP-8800C sphygmomanometers Blood pressure management was overseen at each site by a physician with special expertise in blood-pressure control. Treatment algorithm for titration of dose and the addition of agents, using a step-wise approach. If SBP in comparator group dropped below the lower limit of the target range, patients on antihypertensive medications stopped taking them or had the doses reduced. Indirect BP target threshold comparison.
PRESERVE study group 2021[20] UK	(n=55) Intervention: Systolic BP targets <125mmHg (n=56) Comparator: Systolic BP targets 130-140mmHg	Hypertensive adults with clinical lacunar stroke with an anatomically corresponding lacunar infarct on MRI, in addition to confluent WMH graded >2 on the Fazekas scale. With or without diabetes Aged >40 years; mean 69 (9) CVD diagnoses • 100% stroke • 5% coronary heart disease	At 2 years • All-cause mortality (N events) • Stroke (N events • Acute kidney injury (N events)	During clinic visits, BP was measured in sitting position 3x following a 10 minute rest period in quiet room Recorded BP was mean of second and third measures Both groups also given home blood pressure monitors and asked to perform daily blood pressure readings for at least 3 days prior to each pre-arranged telephone follow-up. [Results presented and used in analysis were CBP readings, but treatment to

Study	Intervention and comparison	Population	Outcomes	Comments
		• 2% peripheral vascular disease Mean (SD) baseline SBP 149(15) vs 148(12) mmHg		target could have been based on HBPM in some]. Treatment algorithms consistent with BHS/NICE Down-titration not mentioned Planned sample size was 180, but recruitment stopped at 111 due to slower than expected recruitment, and a fixed duration grant meaning recruitment could not be continued. Indirect BP target thresholds
RESPECT study group 2019[17] Japan	(n=640) Intervention: BP targets <120/80 mmHg (n=640) Comparator: BP targets <140/90 mmHg (or <130/80 mm Hg for the ~30% of patients with diabetes, chronic kidney disease, or a history of MI.)	Hypertensive adults with a history of stroke with onset 30 days to 3 years previously, with or without diabetes. Aged 50 – 85 years; mean 67.3 (8.8) CVD diagnoses • 97% stroke/TIA • 2.6% coronary heart disease Mean (SD) baseline BP 145(12)/84(11) vs 146(13)/84(10) mmHg	At 3.9 years • All-cause mortality (N events and HR) • Stroke (N events and HR) • Myocardial infarction (N events and HR) • New-onset or worsening heart failure • Coronary intervention or surgery • Number of drugs at end of trial • Worsening renal function • Bone fracture	Office blood pressure monitoring in line with guidelines: properly calibrated mercury/aneroid or electronic manometer seated after rest with measurement taken at least twice, allowing a 1 to 2- minute interval. If the blood pressure levels from these two measurements are extremely different from each other, a third blood pressure reading must be taken. The mean of 2 stable values used. The use of an automatic cuff winding device in the waiting room allowed if carefully supervised to prevent errors. Down titration for standard BP control group for those with DM, CKD, prior MI (if SBP ≤120 at 1 visit or ≤125 at 2 visits) or stroke risk factors (if SBP ≤130 at 1 visit or ≤135 at 2 visits).

Study	Intervention and comparison	Population	Outcomes	Comments
				Trial enrolment stopped early, before reaching the planned sample size, because of slow recruitment and funding cessation. Indirect comparator target in 30%

ACCORD: Action to Control Cardiovascular Risk in Diabetes; BHS: British hypertension society; BP: blood pressure; CBP: clinic blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; HBPM: home blood pressure monitoring; HOT: Hypertension Optimal Treatment; HR: hazard ratio; MI: myocardial infarction; MRI: magnetic resonance imaging; NICE: National Institute for Health and Care Excellence; PAST BP: Prevention After Stroke – Blood Pressure; PRESERVE: PRESsure in established cERebral small VEssel disease; RESPECT: Recurrent stroke prevention clinical outcome study; SBP: systolic blood pressure; SD: standard deviation; SPRINT: Systolic Blood Pressure Intervention Trial; SPS3: Secondary Prevention of Small Subcortical Strokes; TIA: transient ischaemic attack; WMH: white matter hyperintensity.

Table 3: Summary of blood pressure values achieved during trials included in the evidence review

Study	Proportion reaching target during trial		Achieved BP (mmHg)	
	Intervention (lower target)	Control (standard target)	Intervention (lower target)	Control (standard target)
ACCORD study group 2010 (from Saiz 2020[23])	At 1 year 62.2%	At 1 year 71.8%	Final SBP, mean (SD) 119.3 (0.4)	Final SBP, mean (SD) 133.5 (0.4)
HOT study group 1998 (from Saiz 2020[23])	At 1 year 73%	At 1 year 81%	Final DBP, mean (SD) 82 (5)	Final DBP, mean (SD) 85 (5)
PAST BP study group 2016[13, 19]	51%	82%	Final SBP/DBP, mean (SD) 127.4/72.0 (14.8/9.0)	Final SBP/DBP, mean (SD) 129.4/74.4 (14.8/8.9)
SPRINT study group 2015 (from Saiz 2020[23] and Vlachopoulos 2019[24])	At 1 year 54.1%	At 1 year 67.5%	SBP/DBP, mean (SD) – average during follow-up 121.6/65.2 (16.1/12.3)	SBP/DBP, mean (SD) – average during follow-up 134.0/71.4 (15.7/11.9)
SPS3 study group 2013[5, 6]	65%	75%	Final SBP, mean (95% CI) 127 (95% CI 126–128)	Final SBP, mean (95% CI) 138 (95% CI 137–139)
PRESERVE study group 2021[20]	32%	40.7%	Final SBP, mean 126.2	Final SBP, mean 132.5

Study	Proportion reaching target during trial		Achieved BP (mmHg)	
	Intervention (lower target)	Control (standard target)	Intervention (lower target)	Control (standard target)
RESPECT study group 2019[17]	32%	62%	SBP/DBP, mean (95% CI) – average during follow-up 126.7/74.4 (125.9-27.2 / 73.8-75.0)	SBP/DBP, mean (95% CI) – average during follow-up 133.2/77.7 (132.5-33.8 / 77.1-78.4)

ACCORD: Action to Control Cardiovascular Risk in Diabetes; BP: blood pressure; DBP: diastolic blood pressure; HOT: Hypertension Optimal Treatment; HR: hazard ratio; MI: myocardial infarction; PAST BP: Prevention After Stroke – Blood Pressure; PRESERVE: PRESsure in established cERebral small VEssel disease; RESPECT: Recurrent stroke prevention clinical outcome study; SBP: systolic blood pressure; SD: standard deviation; SPRINT: Systolic Blood Pressure Intervention Trial; SPS3: Secondary Prevention of Small Subcortical Strokes.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 4: Clinical evidence summary: lower BP target versus standard BP target in adults aged <80 years

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard BP targets	Risk difference with lower BP targets
All-cause mortality Follow up: range 3.8 years to 4.7 years	4763 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.15 (0.93 to 1.44)	66 per 1,000	10 more per 1,000 (5 fewer to 29 more)
Total cardiovascular events Follow up: range 3.8 years to 4.7 years	4763 (2 RCTs)	⊕⊕◯◯ LOW [d,e]	RR 0.89 (0.75 to 1.04)	133 per 1,000	15 fewer per 1,000 (33 fewer to 5 more)
Resource use: Number of antihypertensive drugs needed per participant at the end of study Follow up: range 3.8 years to 4.7 years	3889 (2 RCTs)	⊕◯◯◯ VERY LOW [b,f,g,h]	-	The mean No. drugs at the end of study was 2.18	MD 0.57 higher (0.26 lower to 1.41 higher)
Participant withdrawals due to adverse effects Follow up: mean 3.8 years	395 (1 RCT)	⊕◯◯◯ VERY LOW [f,I,j]	RR 2.42 (0.29 to 20.54)	8 per 1,000	11 more per 1,000 (6 fewer to 151 more)

a. Majority of the evidence based on post-hoc subgroup analysis of RCT data
b. Majority of the evidence indirect due to BP target threshold definitions and population definition excluded TIA
c. 95% CI crosses the line of no effect
d. Indirect outcome measure: composite including CV event and mortality
e. 95% CI crosses one MID
f. Patients and caregivers not blinded to allocation
g. I^2 = 99%
h. 95%CI crosses one MID (MID= ±0.49)
i. Indirect BP target threshold and population definition excluded TIA
j. 95% CI crosses both MIDs

Table 5: Clinical evidence summary: lower BP target versus standard BP target in a mixed population including adults aged <80 and ≥80 years

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard BP targets	Risk difference with lower BP targets
All-cause mortality Follow up: range 1 year to 3.9 years	6485 (5 RCTs)	⊕⊕◯◯ LOW [a,b]	RR 0.90 (0.74 to 1.09)	63 per 1,000	6 fewer per 1,000 (16 fewer to 6 more)
All-cause mortality (HR) *Follow up: range 3.3 years to 3.9 years[*]*	*5845* *(3 RCTs)*	*⊕⊕◯◯* *LOW [c,d]*	*HR 0.88* *(0.72 to 1.08)*	*69 per 1,000*	*8 fewer per 1,000* *(19 fewer to 5 more)*
Stroke follow up: range 1 year to 3.9 years	6485 (5 RCTs)	⊕⊕◯◯ LOW [c,d]	RR 0.85 (0.71 to 1.03)	69 per 1,000	10 fewer per 1,000 (20 fewer to 0 fewer)[e]

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard BP targets	Risk difference with lower BP targets
Stroke (HR) Follow up: range 3.3 years to 3.9 years[*]	*5845 (3 RCTs)*	*⊕⊕◯◯ LOW [c,d]*	*HR 0.84 (0.69 to 1.02)*	*74 per 1,000*	*11 fewer per 1,000 (22 fewer to 1 more)*
Myocardial infarction Follow up: range 1 year to 3.9 years	6374 (4 RCTs)	⊕◯◯◯ VERY LOW [a,f,g]	RR 1.00 (0.73 to 1.35)	25 per 1,000	0 fewer per 1,000 (7 fewer to 9 more)
Myocardial infarction (HR) Follow up: range 3.3 years to 3.9 years[*]	*5845 (3 RCTs)*	*⊕◯◯◯ VERY LOW [a,f,g]*	*HR 0.96 (0.70 to 1.32)*	*27 per 1,000*	*1 fewer per 1,000 (8 fewer to 9 more)*
Heart failure Follow up: range 3.3 years to 3.9 years	2825 (2 RCTs)	⊕◯◯◯ VERY LOW [f,g,h]	RR 0.75 (0.46 to 1.23)	25 per 1,000	6 fewer per 1,000 (14 fewer to 6 more)
Vascular procedures (coronary intervention or surgery) Follow up: mean 3.9 years	1263 (1 RCT)	⊕⊕◯◯ LOW [g]	RR 0.90 (0.39 to 2.12)	17 per 1,000	2 fewer per 1,000 (11 fewer to 20 more)
Resource use: Number of antihypertensive drugs needed per participant at the end of study Follow up: range 1 year to 3.7 years	4959 (3 RCTs)	⊕◯◯◯ VERY LOW [a,i,j,k]	-	The mean number of drugs needed at the end of study was 1.9	MD 0.62 higher (0.25 higher to 0.99 higher)
Resource use: Mean number of drugs at end of follow up Follow up: mean 3.9 years	1263 (1 RCT)	⊕⊕⊕◯ MODERATE [i,l]	-	The mean number of drugs at end of follow up was 1.6 drugs	MD 1.2 drugs higher
Resource use: Median number of GP visits Follow up: mean 1 year	529 (1 RCT)	⊕◯◯◯ VERY LOW [i,l,m]	-	The median number of GP visits was 1	Median 1 visit higher
Resource use: Median number of practice nurse visits Follow up: mean 1 year	529 (1 RCT)	⊕◯◯◯ VERY LOW [i,l,m]	-	The median number of practice nurse visits was 2	Median 1 visit higher
Resource use (emergency admission) Follow up: mean 1 year	529 (1 RCT)	⊕◯◯◯ VERY LOW [d,m,n]	HR 1.56 (0.84 to 2.90)	7.8% per year	5% higher per year
Participant withdrawals due to adverse effects Follow up: mean 1 year	295 (1 RCT)	⊕◯◯◯ VERY LOW [m,o]	RR 15.56 (2.10 to 115.45)	7 per 1,000	103 more per 1,000 (8 more to 812 more)
AKI Follow up: range 2.0 years to 3.3 years	1673 (2 RCTs)	⊕◯◯◯ VERY LOW [d,f,p]	RR 1.49 (0.98 to 2.25)	42 per 1,000	20 more per 1,000 (0 fewer to 40 more)[e]

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard BP targets	Risk difference with lower BP targets
Worsening renal function Follow up: mean 3.9 years	1293 (1 RCT)	⊕◯◯◯ VERY LOW [g,n,q]	RR 5.70 (0.69 to 47.22)	2 per 1,000	7 more per 1,000 (0 fewer to 73 more)
Injurious falls Follow up: range 1 years to 3.9 years	3354 (3 RCTs)	⊕◯◯◯ VERY LOW [f,g,r]	RR 0.89 (0.59 to 1.35)	27 per 1,000	3 fewer per 1,000 (11 fewer to 10 more)

** For these outcomes both the dichotomous and time-to-event data are reported, but the primary measure for decision-making was the dichotomous data because there was very little difference in the effect estimates from the hazard ratios and risk ratios, while the risk ratio analysis has the benefit of including all available data.*
a. Majority of the evidence indirect due to BP target threshold definitions and/or method of blood pressure measurement
b. 95% CI crosses the line of no effect
c. Majority of the evidence indirect due to BP target threshold definitions
d. 95% CI crosses one MID
e. Calculated from risk difference because zero events in one arm of one trial
f. Majority of the evidence at high risk of attrition bias
g. 95% CI crosses both MIDs
h. Majority of the evidence indirect due to BP target threshold definitions and method of blood pressure measurement
i. Patients and caregivers not blinded to allocation
j. I^2 = 96%
k. 95% crosses one MID (MID=0.7)
l. Imprecision could not be assessed
m. Indirect BP target threshold and hypertension definition
n. High risk of attrition bias
o. Patients and caregivers not blinded to allocation and high risk of attrition bias
p. Majority of the evidence indirect due to method of blood pressure measurement
q. Indirect BP target threshold
r. Majority of the evidence indirect due to BP target threshold definitions and/or method of blood pressure measurement and/or outcome definition

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with a relevant comparison in people with stroke/TIA was included in this review.[22] This was based on the PAST-BP RCT that was included in the mixed population including adults aged <80 and ≥80 years stratum in the clinical review. No health economic studies were included related to the population strata of <80 year and ≥80 years. This is summarised in the health economic evidence profile below (Table 6) and the health economic evidence table in Appendix H.

No health economic studies in people with other types of CVD were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

Table 6: Health economic evidence profile: lower blood pressure target versus standard target in a mixed population including adults aged <80 and ≥80 years

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Pendaloza-Ramos 2016[22] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Probabilistic decision analytic model utilising patient-level data from the PAST-BP[19] RCT (events modelled included new stroke, MI and unstable angina) • Cost-utility analysis (QALYs) • Population: previous stroke/TIA and SBP ≥125mmHg • Comparators ○ Standard target (<140mmHg systolic blood pressure) ○ Lower target (<130mmHg systolic blood pressure or 10mmHg reduction from baseline if this was <140mmHg) • Time horizon: lifetime	-£169[(c)]	0.08 QALYs	Lower target dominant (lower costs and higher QALYs)	The lower target was no longer cost effective if the lower bound of the 95% CI for BP reduction was used, if a time horizon of only 1 year was used and if intensive BP lowering is associated with a 2% or more reduction in quality of life (it remains less costly because of the reduction in cardiovascular events but also results in less QALYs).

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; RCT = randomised controlled trial; SBP = systolic blood pressure; TIA = transient ischemic attack.

(a) Population doesn't exactly match protocol – not all hypertensive. Intervention doesn't exactly match protocol. UK resource use from 2009-12 (PAST-BP) and older (published sources) and 2011/12 costs may not reflect current UK context.

(b) Based on one of several studies included in clinical review and so does not reflect all available clinical evidence. Model uses blood pressure reduction from clinical trial to model differences in clinical events rather than direct evidence of effect on clinical events as specified in clinical review protocol for outcomes. Unclear if baseline event probabilities are from best available source; based on PROGRESS RCT which recruited from Asia, Australia and Europe 1995 to 2001 and so may not reflect current real-world event rates for England; rationale for selection not described. PAST-BP reported an increase in emergency admissions with the lower target but this does not appear to be included in the cost analysis. Uncertainty around baseline event probabilities, blood pressure reduction and the relationship between blood pressure reduction and reduction in clinical events do not appear to be incorporated into the probabilistic analysis and so uncertainty will be underestimated.

(c) 2011/12 costs. Cost components incorporated: antihypertensive drugs, GP and nurse consultations and acute and long terms costs of cardiovascular events.

1.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Lower targets may require additional resource use such as more antihypertensive drugs and more healthcare visits. Some illustrative unit costs of antihypertensive drugs are provided below in Table 7. Usual daily dose is based on BNF dosing information for hypertension. Typical primary care consultation costs are provided in Table 8.

Table 7: Antihypertensive drug costs

Drug	Usual daily dose	Cost per year
ACE inhibitors		
Captopril	12.5-150mg	£12 to £33
Enalapril maleate	20mg	£174
Fosinopril sodium	10-40mg	£65 to £266
Imidapril hydrochloride	2.5-10mg	£42 to £94
Lisinopril	20mg	£16
Perindopril arginine	2.5-10mg	£54 to £130
Perindopril erbumine	2-8mg	£26 to £35
Quinapril	20-40mg	£127 to £141
Ramipril	1.25-10mg	£15 to £22
Trandolapril	1-2mg	£39 to £263
Angiotensin II receptor blockers		
Azilsartan medoxomil	20-80mg	£219 to £260
Candesartan cilexetil	8mg daily	£20
Eprosartan	600mg	£237
Irbesartan	75-300mg	£32 to £68
Losartan potassium	25-100mg	£17 to £23
Olmesartan medoxomil	10mg-20mg	£42 to £45
Telmisartan	20-80mg	£29 to £49
Valsartan	80-320mg	£123 to £237
Beta blockers		
Acebutolol	400-800mg	£243 to £485
Atenolol	25-50mg	£11 to £12
Bisoprolol fumarate	5-10mg	£13 to £17
Celiprolol hydrochloride	200-400mg	£122 to £212
Metoprolol tartrate	100-200mg	£33 to £69
Nebivolol	2.5-5mg	£26 to £69
Calcium channel blockers		
Amlodipine	5-10mg	£14 to £14
Diltiazem hydrochloride	Depends on formulation (MR)	£62 to £222
Felodipine	5-10mg	£55 to £74
Lacidipine	2-6mg	£28 to £41
Lercanidipine hydrochloride	10-20mg	£26 to £28
Nifedipine	Depends on formulation (MR)	£47 to £350
Verapamil hydrochloride	240-480mg (IR and MR formulations)	£39 to £617
Diuretics		

Drug	Usual daily dose	Cost per year
Chlortalidone	25-50mg	£536 to £1071
Indapamide	2.5mg / MR 1.5mg	£24 to £41
Xipamide	20mg	£51

Abbreviations: ACE = Angiotensin-converting enzyme; IR = immediate release; MR = modified-release.

Source: BNF 19th July 2021.[7] Usual daily dose based on dosing information for hypertension indication. Drug tariff costs (as listed in BNF) used in costing.

Table 8: Primary care visit costs

Drug	Cost per hour	Cost per hour of patient contact	Cost per appointment
GP	£133	£205	£31 (9.22 minutes)
Practice nurse	£41	£54	£13.82 (15.5 minutes)

Source: PSSRU unit costs 2020.[4] Costs include salary, salary oncosts, overheads (management and other non-care staff costs including administration and estates staff), capital overheads and qualification costs (excluding those related to living expenses and lost production). GP units costs are excluding direct care staff. Practice nurse costs per hour of patient contact and average appointment times were not available in the 2020 report and so were calculated using 2020 unit costs and data from the 2015 report about the ratio of direct to indirect time (1:0.30) and average consultation time (15.5 minutes).[9]

1.1.11 Evidence statements

Economic

- One cost–utility analysis found that a lower blood pressure target was dominant (cost saving and higher QALYs) compared to a standard target in people with a history of stroke/TIA and SBP ≥125 mmHg. This analysis was assessed as partially applicable with potentially serious limitations.
- No relevant economic evaluations were identified for CVD other than stroke/TIA.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The following outcomes were included:

- All-cause mortality
- Health-related quality of life
- Stroke
- Acute coronary syndrome (ACS, including myocardial infarction)
- Heart failure needing hospitalisation
- Vascular procedures
- Discontinuation or dose reduction due to side effects
- Resource use
- Side effect 1: Acute kidney injury
- Side effect 2: Deterioration in eGFR >30%
- Side effect 3: Injurious falls.

The composite outcome of cardiovascular events during follow up was included if no myocardial infarction (MI)/ACS and stroke data were available and the composite outcome of coronary heart disease events during follow up if no MI/ACS data were available. Data on the number of people achieving the blood pressure target and the final blood pressure values were considered as trial characteristics and not analysed as outcomes.

No data were available for health-related quality of life, nor any data for the age stratum of ≥80 years.

1.1.12.2 The quality of the evidence

The majority of the evidence was of low or very low quality. Common reasons for downgrading included indirectness relating to the blood pressure target thresholds, which in most cases did not exactly match those specified in the protocol, and imprecision. Additionally, subjective outcomes were at high risk of bias because blinding of study participants and caregivers was not possible. The committee noted that the number of participants was relatively low, which likely contributed to the imprecision in the results.

These limitations in the evidence reduced the confidence of the committee in the results. Given that the absolute risk differences were small, there was uncertainty around these estimates (with signals of both benefit and harm) and the fact that the blood pressure target thresholds were not directly relevant to those specified in the review protocol, the committee agreed the evidence was insufficiently robust to recommend a more intensive blood pressure target in adults with hypertension and established cardiovascular disease compared to hypertensive individuals without CVD.

There were no data specifically for adults aged 80 years and over, only mixed populations where people over 80 were not excluded, however the mean age of participants suggested most were aged under 80. There was also no available evidence for adults with aortic aneurysm and therefore, research recommendations have been developed for these groups.

1.1.12.3 Benefits and harms

Age <80 years

The inclusion criteria for 2 of the trials limited participants to adults aged <80 or ≤80 and so these trials have been analysed separately according to the prespecified age strata.

A possible clinical harm of a lower blood pressure target was identified for mortality, but there was uncertainty around this estimate, and it was not consistent with the reported total cardiovascular events, which showed the opposite direction of effect. The committee could not reconcile this inconsistency, and agreed that the relatively small number of participants would have caused uncertainty in the estimates for these outcomes, which taken together suggest no real clinical difference between standard and lower blood pressure targets. There was also no clinical difference in the number of withdrawals due to adverse events. However, the resource use was greater in the group with lower blood pressure targets, with the mean number of anti-hypertensive drugs required at the end of the study being 0.57 more. Inconsistency between the 2 studies was noted for this outcome, with the mean difference being 1.00 in the ACCORD trial and 0.15 in the HOT trial.

Mixed age <80 and ≥80 years

The remaining 5 trials included adults both above and below 80 years of age, although the majority were likely to have been <80 years old based on the stated mean and standard deviation of the age of the included participants. Therefore, a research recommendation was made for adults aged 80 and over as no specific evidence was available.

Among these trials, 4 of which were in stroke/TIA populations, there was a small clinical benefit of a lower blood pressure target for all-cause mortality and stroke. For stroke, it was noted that the 1 trial that excluded adults with a prior stroke (SPRINT) showed the opposite direction of effect, with fewer strokes occurring during follow-up in the standard target group. However, there was no clear heterogeneity in the meta-analysis, and it would not be appropriate to conduct a post-hoc subgroup analysis with only a single study in one of the groups. It was discussed that the benefit of lower blood pressure targets for reduced

incidence of stroke may be greater in the context of recurrent stroke for those with a prior stroke or TIA. Nevertheless, the SPRINT study only contributed 5.8% of the weight of the meta-analysis so the effect estimate would not change greatly if this study was removed. The committee discussed the 2016 Intercollegiate Stroke Working Party (ICSWP) guideline recommendation for a target systolic blood pressure of 130 mmHg for people with a history of stroke or TIA (except for people with severe bilateral carotid artery stenosis). They discussed that part of the reason this differs from the recommendation made as a result of the evidence review presented here is that this review, unlike the review in the ICSWP guideline, focussed on randomised trials of different targets limited to people with hypertension and existing cardiovascular disease. Although the evidence reviewed here did also show a signal for benefit for lower blood pressure targets in the stroke population, there was also some evidence of harm. The committee agreed the evidence currently available did not support an active recommendation for lower blood pressure targets after stroke because the absolute risk differences for benefit were small, resource use would be increased and there was not enough data to confidently assess the possible harms. Therefore, a research recommendation was made for this population.

There was evidence to suggest clinically important harms of a lower blood pressure target compared with a standard blood pressure target as shown by increased numbers of participant withdrawals and acute kidney injury events. There was also evidence of increased resource use in the intensive blood pressure target group, with a higher number of anti-hypertensive drugs being needed as well as an increased number of GP and practice nurse visits and emergency admissions. No clinical difference was seen for the remaining reported outcomes, which were myocardial infarction, heart failure, vascular procedures, worsening renal function and injurious falls. The outcome of worsening renal function was discussed, with the committee noting that the definition used in the study was not a standard threshold but may reflect an important concern in some patients depending on the baseline eGFR level. However, there was too much uncertainty in the effect to see any clinical difference.

Summary

Taking the body of evidence together and looking across all available outcome data, the committee agreed that the evidence did not support a recommendation for lower blood pressure targets in adults with hypertension and established cardiovascular disease, compared to those without established cardiovascular disease. The available data were limited in terms of quality and quantity, and although some studies suggested important clinical benefit from more intensive blood pressure control (particularly in people with prior stroke/TIA), others identified associated harm in terms of acute kidney injury withdrawal due to adverse events. Given the absence of high quality data and the inconsistent findings concerning clinical outcomes, the committee could not recommend a more intensive blood pressure treatment target for people with established CVD. The committee discussed that this is an active area of research and as more high quality evidence becomes available this may prompt review of this recommendation. Overall, it was agreed by the committee that the current body of evidence does not support a lower blood pressure treatment target for hypertensive patients with CVD compared to those without, and it was agreed that any review of the recommendations in the general hypertension population should be matched for the population with established CVD.

Although there was insufficiently robust evidence to change the recommended blood pressure targets, it was evident that in the included studies systolic blood pressure levels were reduced well below 140 mmHg even in the standard blood pressure target groups, with the range being 129.4 mmHg to 138 mmHg. The committee agreed that this supports the need to emphasise achieving a clinic blood pressure target of below 140/90 mmHg, as per the recommendations for people without established CVD. The committee discussed including a range of blood pressure targets within the recommendation, for example, an optimum range of 130/80 to 139/89 mmHg. However, it was agreed this may imply 130 mmHg is a strict lower limit, which could inadvertently lead to excessively cautious blood

pressure management. The committee also noted that across all trials the proportion reaching the randomised blood pressure target was lower in the intervention arm. The final or average achieved systolic blood pressure in the intervention arm was reported as <130 mmHg and in the control arm was <140 mmHg. However, the committee discussed that this was indicative of the active management in a clinical trial setting compared to the real-world difficulties in achieving guideline-driven blood pressure levels.

The committee therefore agreed not to state a range, but to emphasise the importance of reducing clinic blood pressure below 140/90 mmHg in those aged <80 years such that neither patients nor practitioners will be accepting of clinic blood pressure values of 140/90 mmHg or higher. Similarly, in those aged 80 years and over the importance of reducing clinic blood pressure below 150/90 mmHg was emphasised by rewording the recommendation.

1.1.12.4 Cost effectiveness and resource use

One economic evaluation related to blood pressure targets in people with established cardiovascular disease was included. This compared a lower versus standard target in people with a history of stoke or TIA and a SBP above 125 mmHg based on the PAST-BP RCT that was included in the clinical review. No studies were identified in other cardiovascular disease populations.

This analysis took a UK perspective and found that a lower target was cost effective as it reduced costs and increased QALYs over a lifetime horizon. Higher intervention costs with a lower target were offset by savings from cardiovascular events avoided in the model. The committee discussed the limitations of the analysis.

The committee noted that the population and intervention (<130 mmHg SBP or 10 mmHg reduction from baseline if this was <140 mmHg) in the PAST-BP RCT did not exactly match the review protocol (population not all hypertensive [48% had SBP<140 at baseline] and lower SBP target slightly different from protocol [<130 mm Hg]), and, as such, was considered indirect evidence.

Intervention costs in the published economic evaluation were based on analysis of patient-level data from PAST-BP and included drug costs, GP visits, and practice nurse visits. Overall intervention costs were £44 per year higher with the lower target. The committee noted that the difference in number of drugs in PAST-BP was lower than from the meta-analysis of all studies in the clinical evidence review (mean difference 0.20 drugs in PAST-BP and around 0.6 based on all available data). This may mean that this analysis underestimates the difference in intervention costs with a lower target. The committee also noted that while primary care visits may partially account for the potential impact of additional adverse effects or monitoring of additional drugs and/or a lower target, the PAST-BP RCT reported an increase in emergency admissions with the lower target but that this does not appear to be incorporated in the model. The committee discussed that the clinical evidence review suggested there may be a harm for a lower target in terms of AKI which could plausibly result in additional emergency admissions. This may also mean that the difference in intervention costs could be underestimated.

The committee discussed how differences in clinical events were modelled in the analysis. As the PAST-BP RCT was not powered to look at cardiovascular events, the model uses the change in blood pressure from baseline with the standard and lower targets to estimate the effect on cardiovascular events. Blood pressure reduction at 12 months was converted to a relative risk for coronary heart disease events and stroke using a published meta-analysis by Law et al . These relative risks were applied to baseline probabilities of cardiovascular events estimated based on the PROGRESS RCT to calculate cardiovascular events with each target. It was assumed treatment effect was maintained beyond 1 year. As blood pressure reduction from baseline was greater with the lower target, this results in a greater reduction in cardiovascular events and mortality.

It was noted that the use of RCT data for the baseline probabilities of cardiovascular events in the model may underestimate real-world risks as RCTs enrol a selected population often excluding people at higher risk. However, it was also noted that the PROGRESS RCT recruited from 1995 to 2001, and so may overestimate current event probabilities as outcomes post-stroke have improved over time.

The committee also noted that the clinical review protocol specified data on actual clinical events, not the surrogate outcome of blood pressure reduction. However, it was agreed that the model could still potentially be helpful if the treatment effects applied were consistent with the clinical evidence review estimates from the broader evidence base. This was considered by comparing the meta-analysed relative treatment effects from the guideline clinical evidence review with the model-relative treatment effects. The latter was calculated from the relative risks applied for the lower and standard target reported in the model publication. In the model, the lower target reduced blood pressure and also stroke, MI, unstable angina and mortality. In the clinical review some evidence was seen for reduction in stroke events. The evidence about mortality was however mixed and there was no evidence of a reduction in MI. A potential harm was also seen in the clinical evidence review in terms of AKI that was not considered in the cost-effectiveness model. Uncertainty around baseline event probabilities and treatment effects in terms of blood pressure reduction, or the relationship between blood pressure reduction and reduction in clinical events, are not stated as being incorporated in the probabilistic analysis, and so uncertainty is likely to be underestimated in the analysis.

Overall, the committee agreed that while the published cost-effectiveness analysis showed there was potential for a lower target to be cost effective in a stroke/TIA population, there were a number of limitations of the analysis that could impact the estimation of cost and QALYs and so cost-effectiveness. In addition, given the overall clinical evidence was not considered sufficiently robust to be confident about the clinical effects of a lower target, this also translates into uncertainty in cost effectiveness. No cost effectiveness evidence was identified in other cardiovascular disease populations.

The committee agreed it was unlikely that there would be a substantial change in practice or increase in resource use in the NHS in England from not recommending a different blood pressure target for people with compared to those without cardiovascular disease, given that the existing blood pressure targets reflect current practice for most types of cardiovascular disease. It was noted that the current ICSWP stroke guideline advocates a lower blood pressure target for patients following acute stroke. National quality indicators used in primary care do not use a lower blood pressure target for people with cardiovascular disease (including stroke/TIA), so it was considered likely that using the same target was in keeping with existing, majority practice.

1.1.12.5 Other factors the committee took into account

The committee noted that some of the included trials were based on participants recruited over a decade ago, when blood pressure and cardiovascular disease management were less advanced than they are now. Consequently, the event rates in these trials were higher than would be expected in current clinical practice. However, the impact of this on the effect estimate should be minimal as it applies to both the intervention and control groups.

The committee also discussed the importance of keeping the recommendation wording simple and clear to facilitate implementation.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.23 and the research recommendations on blood pressure targets for people over 80, people with aortic aneurysm and for people with prior stroke.

1.1.14 References

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Appendices

Appendix A – Review protocol

Review protocol for blood pressure targets

ID	Field	Content
0.	PROSPERO registration number	CRD42021273025
1.	Review title	Blood pressure targets for people with established cardiovascular disease
2.	Review question	What are the optimum blood pressure targets for adults with diagnosed primary hypertension and established cardiovascular disease?
3.	Objective	To establish which blood pressure targets should be aimed for in people with established cardiovascular disease and hypertension.
4.	Searches	**Key paper:** Saiz et al., Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane database of Systematic Reviews. https://doi.org/10.1002/14651858.CD010315.pub4 The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

		• 2019-present: to update the search in Saiz et al Cochrane review. • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Hypertension in adults with established cardiovascular disease.
6.	Population	**Inclusion:** Adults (over 18 years) with diagnosed primary hypertension and established cardiovascular disease. Stratify by age <80 years and age ≥80 years Established CVD includes past medical history of:

		• **ischaemic heart disease:** acute coronary syndrome, for example myocardial infarction, (silent or symptomatic), angina with confirmed underlying coronary artery disease, previous percutaneous coronary intervention, or previous coronary artery bypass graft surgery. • **cerebrovascular disease**: stroke and/or TIA, or haemorrhage or radiological evidence of prior stroke • **peripheral vascular disease**: symptomatic claudication and/or confirmed peripheral vascular disease on angiography or abnormal ABPI (<0.9) • **aortic aneurysm** • **heart failure** Studies with <80% of participants matching the target population will be excluded, unless they report subgroup data for the target population (those with established CVD and hypertension). Studies with mixed populations including people with different CVD diagnoses will be included, along with studies in people with a specific CVD diagnosis. **Exclusions:** • Studies including participants with type 1 diabetes • Studies including participants with chronic kidney disease that indicates the need for lower blood pressure targets (chronic kidney disease and type 2 diabetes; or ACR 70 mg/mmol or more) • Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (such as Conn's adenoma, phaeochromocytoma, renovascular hypertension) • Ocular HT, pulmonary HT, acute HT, malignant HT, portal HT, and intracranial HT • Acute and malignant hypertension • Orthostatic hypertension • Pregnant women • Children (age under 18 years)
7.	Intervention (lower blood pressure treatment target)	**Blood pressure targets for those aged <80 years** • Systolic blood pressure target: ○ clinic measurement 130 mmHg or less; ○ home, ambulatory or unattended/automated clinic measurement 125 or less And/or • Diastolic blood pressure target:

		○ clinic measurement 80 mmHg or less ○ home, ambulatory or unattended/automated clinic measurement 75 mmHg or less **Blood pressure targets for those aged ≥80 years** • Systolic blood pressure target: ○ clinic measurement below 140 mmHg ○ home, ambulatory or unattended/automated clinic measurement below 135 mmHg And/or • Diastolic blood pressure target: ○ clinic measurement below 80 mmHg ○ home, ambulatory or unattended/automated clinic measurement below 75 mmHg Combining data: • Any blood pressure targets from different studies below the thresholds stated will be pooled as the intervention group (for example clinic SBP target <130 would be pooled with clinic SBP target <120). • Studies using clinic measurements will be pooled with studies using equivalent unattended/automated, home or ambulatory measurements as defined above • Studies specifying a lower systolic blood pressure as the target will be pooled with those specifying a lower diastolic blood pressure target because the aim is still to lower blood pressure more intensively Note that treatment must be received for a minimum of 1 year. Studies with <80% of participants matching the intervention of interest will be excluded.
8.	Comparator (standard treatment target)	**Blood pressure targets for those aged <80 years** • Systolic blood pressure target ○ clinic measurement below 140 mmHg ○ home or ambulatory measurement below 135 mmHg and/or • Diastolic blood pressure target: ○ clinic measurement below 90 mmHg ○ home or ambulatory measurement below 85 mmHg

		Blood pressure targets for those aged ≥80 years • Systolic blood pressure target: ○ clinic measurement below 150 mmHg ○ home or ambulatory measurement below 145 mmHg and/or • Diastolic blood pressure target: ○ clinic measurement below 90 mmHg ○ home or ambulatory measurement below 85 mmHg Note that treatment must be received for a minimum of 1 year
9.	Types of study to be included	**Inclusion** RCTs, subgroup analyses from RCTs and systematic reviews of RCTs Published network meta-analyses and individual participant data meta-analyses will be considered for inclusion. **Exclusion** Cross-over RCTs Non-randomised studies
10.	Other exclusion criteria	Mean blood pressure thresholds/targets Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Follow-up time <12 months.
11.	Context	A review of the evidence is needed to examine whether people with established cardiovascular disease should have different hypertension treatment targets. This will add to the existing evidence in NG136.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted.

		• All-cause mortality • Health-related quality of life • Stroke (ischaemic or primary cerebral haemorrhage) • Acute coronary syndrome (e.g. myocardial infarction, unstable angina) • Heart failure needing hospitalisation • Vascular procedures (including lower limb revascularisation, coronary and carotid artery procedures) • Discontinuation or dose reduction due to side effects • Resource use (e.g. number of pills, GP visits for BP checks, referral to specialist clinics, emergency admissions) • Side effect 1: Acute kidney injury • Side effect 2: Deterioration in eGFR >30% • Side effect 3: Injurious falls • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data] To be extracted and presented in study details, not as outcomes: • Number of patients reaching target • Final BP values
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data

		• a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Systematic reviews will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist and randomised controlled trials using Cochrane RoB (2.0).
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. If the same outcome is reported on different numerical scales the standardised mean difference will be used. This is considered to be a new review question owing to the different population from NG136. Therefore, any outcome data from this review will not be meta-analysed with the data in NG136. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If the data identified are sufficient to undertake a network meta-analysis, this option will be discussed with the committee and NICE. WinBUGS will be used for network meta-analysis, if this is agreed to be required.

16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Age within <80 years stratum (under 55, 55–79) • Family origin (black African and African-Caribbean, South Asian, mixed, Other [e.g. White, other Asian heritage]) • Presence or absence of type 2 diabetes • Time from last cardiovascular event to randomisation (<1 year, 1-3 years, >3 years) • Severity of hypertension (moderate [140–159/90–99 mmHg] versus severe [≥160/100 mmHg]) • Presence or absence of CKD • Method of blood pressure measurement (clinic vs home/ambulatory vs unattended or automated office measurement) • Lower treatment target threshold ○ Clinic SBP target: <120, 120-130mmHg ○ Clinic DBP target: <75, 75-80 mmHg	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	August 2021	
21.	Anticipated completion date	March 2022	

<table>
<tr><td>22.</td><td>Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td></td><td></td><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
HTAupdate@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and National Guideline Centre.</td></tr>
<tr><td>24.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:
Guideline lead: Serena Carville
Systematic reviewer: Eleanor Samarasekera
Health economist: Kate Lovibond
Information specialist: Lina Gulhane</td></tr>
<tr><td>25.</td><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</td></tr>
</table>

26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10177	
28.	Other registration details	NA	
29.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=273025	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Hypertension; cardiovascular disease; blood pressure targets	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☐	Ongoing

		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years • Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[21] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- What are the optimum blood pressure targets for adults with diagnosed primary hypertension and established cardiovascular disease?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[21]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical literature search strategy

Table 9: Clinical search summary

Search adapted from the Cochrane review:

Blood pressure targets for the treatment of people with hypertension and cardiovascular disease[23]

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010315.pub4/appendices#CD010315-sec-0084

Database	Dates searched	Search filters and limits applied
Medline (OVID)	2019 – 23 June 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	2019 – 23 June 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews from 2019 – 23 June 2021 Issue 6 of 12, June 2021 CENTRAL from 2019 – 23 June 2021 Issue 6 of 12, June 2021	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	2019 – 23 June 2021	Systematic review Exclusions (Cochrane reviews) English language
Lilacs	2019 – 23 June 2021	Randomised controlled trials Systematic review studies

Medline (Ovid) search terms

1.	exp cardiovascular diseases/
2.	((heart or myocardial) adj5 (attack* or disease* or infarc*)).tw,kf.
3.	(coronary adj5 (disease* or syndrome*)).tw,kf.
4.	((cardiovascular or peripheral or vascular) adj5 disease*).tw,kf.
5.	atrial fibril*.tw,kf.
6.	((cardiac or heart) adj failure).tw,kf.
7.	angina*.tw,kf.
8.	exp ischemia/
9.	(ischaemi* or ischemi*).tw,kf.
10.	exp stroke/
11.	(CVA or poststroke or post stroke or stroke or strokes).tw,kf.
12.	apoplexy.tw,kf.
13.	cerebrovascul*.tw,kf.

14.	cerebral vascular.tw,kf.
15.	((brain* or cerebral* or lacunar) adj2 (accident* or infarct*)).tw,kf.
16.	or/1-15
17.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw,kf.
18.	hypertension/
19.	essential hypertension/
20.	(antihypertens* or hypertens*).tw,kf.
21.	exp blood pressure/
22.	(blood pressure or bloodpressure).tw,kf.
23.	or/18-22
24.	16 and 17 and 23
25.	letter/
26.	editorial/
27.	news/
28.	exp historical article/
29.	Anecdotes as Topic/
30.	comment/
31.	case report/
32.	(letter or comment*).ti.
33.	or/25-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animals/ not humans/
37.	exp Animals, Laboratory/
38.	exp Animal Experimentation/
39.	exp Models, Animal/
40.	exp Rodentia/
41.	(rat or rats or mouse or mice or rodent*).ti.
42.	or/35-41
43.	24 not 42
44.	limit 43 to English language
45.	randomized controlled trial.pt.
46.	controlled clinical trial.pt.
47.	randomi#ed.ab.
48.	placebo.ab.
49.	randomly.ab.
50.	clinical trials as topic.sh.
51.	trial.ti.
52.	or/45-51
53.	Meta-Analysis/
54.	Meta-Analysis as Topic/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	44 and (52 or 63)
65.	(2019* or 202*).ed,ep,yr..
66.	64 and 65

Embase (Ovid) search terms

1.	exp cardiovascular disease/
2.	((heart or myocardial) adj5 (attack* or disease* or infarc*)).tw.
3.	(coronary adj5 (disease* or syndrome*)).tw.
4.	((cardiovascular or peripheral or vascular) adj5 disease*).tw.
5.	atrial fibril*.tw.
6.	((cardiac or heart) adj failure).tw.
7.	angina*.tw.
8.	exp ischemia/
9.	(ischaemi* or ischemi*).tw.
10.	exp stroke/
11.	(CVA or poststroke or post stroke or stroke or strokes).tw.
12.	apoplexy.tw.
13.	cerebrovascul*.tw.
14.	cerebral vascular.tw.
15.	((brain* or cerebral* or lacunar) adj2 (accident* or infarct*)).tw.
16.	or/1-15
17.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw.
18.	hypertension/
19.	(antihypertens* or hypertens*).tw.
20.	exp blood pressure/
21.	(blood pressure or bloodpressure).mp.
22.	or/18-21
23.	16 and 17 and 22
24.	letter.pt. or letter/
25.	note.pt.
26.	editorial.pt.
27.	case report/ or case study/
28.	(letter or comment*).ti.
29.	(conference abstract or conference paper).pt.
30.	or/24-29
31.	randomized controlled trial/ or random*.ti,ab.
32.	30 not 31
33.	animal/ not human/

34.	nonhuman/
35.	exp Animal Experiment/
36.	exp Experimental Animal/
37.	animal model/
38.	exp Rodent/
39.	(rat or rats or mouse or mice or rodent*).ti.
40.	or/32-39
41.	23 not 40
42.	limit 41 to English language
43.	random*.ti,ab.
44.	factorial*.ti,ab.
45.	(crossover* or cross over*).ti,ab.
46.	((doubl* or singl*) adj blind*).ti,ab.
47.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48.	crossover procedure/
49.	single blind procedure/
50.	randomized controlled trial/
51.	double blind procedure/
52.	or/43-51
53.	systematic review/
54.	Meta-Analysis/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	42 and (52 or 63)
65.	(2019* or 202*).dc,yr.
66.	64 and 65

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] explode all trees
#2.	((heart or myocardial) near/5 (attack* or disease* or infarc*)):ti,ab
#3.	(coronary near/5 (disease* or syndrome*)):ti,ab
#4.	((cardiovascular or peripheral or vascular) near/5 disease*):ti,ab
#5.	atrial fibril*:ti,ab
#6.	((cardiac or heart) next failure):ti,ab
#7.	angina*:ti,ab
#8.	MeSH descriptor: [Ischemia] explode all trees
#9.	(ischaemi* or ischemi*):ti,ab
#10.	MeSH descriptor: [Stroke] explode all trees

#11.	(CVA or poststroke or post stroke or stroke or strokes):ti,ab
#12.	apoplexy:ti,ab
#13.	cerebrovascul*:ti,ab
#14.	cerebral vascular:ti,ab
#15.	((brain* or cerebral* or lacunar) near/2 (accident* or infarct*)):ti,ab
#16.	(or #1-#15)
#17.	((goal* or intensive* or strict* or target* or tight* or optimum or optimal) near/6 (antihypertensive* or anti hypertensive* or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)):ti,ab
#18.	MeSH descriptor: [Hypertension] explode all trees
#19.	MeSH descriptor: [Essential Hypertension] explode all trees
#20.	(antihypertens* or hypertens*):ti,ab
#21.	MeSH descriptor: [Blood Pressure] explode all trees
#22.	(blood pressure or bloodpressure):ti,ab
#23.	(or #18-#22)
#24.	#16 and #17 and #23 with Cochrane Library publication date Between Nov 2019 and Jul 2021
#25.	conference:pt or (clinicaltrials or trialsearch):so
#26.	#24 not #25

Epistemonikos search terms

1.	(((cardiovascular disease?) OR (heart attack*) OR (myocardial infarct*) OR (heart disease*) OR (myocardial disease*) OR (coronary disease*) OR (coronary syndrome*) OR (cardiovascular disease*) OR (peripheral disease*) OR (vascular disease*) OR (atrial fibril*) OR (cardiac failure) OR (heart failure) OR (angina*) OR (ischaemi*) OR (ischemi*) OR (stroke*) OR (cva) OR (poststroke) OR (post-stroke) OR (apoplexy) OR (cerebrovascul*) OR (cerebral vascular) OR (brain* accident*) OR (brain infarct*) OR (cerebral* accident*) OR (cerebral* infarct*) OR (lacunar accident*) OR (lacunar infarct*)) AND ((intensive* bp) OR (intensive* dbp) OR (intensive* blood pressure?) OR (intensive* sbp) OR (strict* bp) OR (strict* dbp) OR (strict* blood pressure?) OR (strict* sbp) OR (target* bp) OR (target* dbp) OR (target* blood pressure?) OR (target* sbp) OR (tight* bp) OR (tight* dbp) OR (tight* blood pressure?) OR (tight* sbp)) AND ((hypertension) OR (hypertens*) OR (blood pressure) OR (bloodpressure)) AND (((pt:”randomised controlled trial”) OR (pt:”controlled clinical trial”) OR (ab:”randomi?ed”) OR (ab:”placebo”) OR (clinical trials) OR (ab:”randomly”) OR (ti:”trial”)) AND NOT ((animals) AND NOT (humans AND animals)))) AND (type_of_study:("clinical_trials" OR "systematic_reviews") AND la:("en")) AND (year_cluster:[2019 TO 2021])

Lilacs search terms

1.	(advanced_title_en:((advanced_title_en:(goal* OR intensive* OR strict* OR target* OR tight* OR optimum OR optimal) OR advanced_abstract_en:(goal* OR intensive* OR strict* OR target* OR tight* OR optimum OR optimal)) AND (advanced_title_en:(antihypertensive* OR anti hypertensive* OR bp OR control OR dbp OR diastolic OR pressure* OR sbp OR systolic OR treat*) OR advanced_abstract_en:(antihypertensive* OR anti hypertensive* OR bp OR control OR dbp OR diastolic OR pressure* OR sbp OR systolic OR treat*))) OR advanced_abstract_en:((advanced_title_en:(goal* OR intensive* OR strict* OR target* OR tight* OR optimum OR optimal) OR advanced_abstract_en:(goal* OR intensive* OR strict* OR target* OR tight* OR optimum OR optimal)) AND (advanced_title_en:(antihypertensive* OR anti hypertensive* OR bp OR control OR dbp OR diastolic OR pressure* OR sbp OR systolic OR treat*) OR advanced_abstract_en:(antihypertensive* OR anti hypertensive* OR bp OR control OR dbp OR diastolic OR pressure* OR sbp OR systolic OR treat*)))) AND (advanced_title_en:(antihypertens* OR hypertens* OR blood pressure OR bloodpressure) OR advanced_abstract_en:(antihypertens* OR hypertens* OR blood pressure OR bloodpressure))

Table 2: Summary of additional TIA and aortic aneurysm search

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 16 August 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 16 August 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews from Inception to 16 August 2021 Issue 8 of 12, August 2021 CENTRAL from Inception to 16 August 2021 Issue 8 of 12, August 2021	Exclusions (clinical trials, conference abstracts)

Medline (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	exp Brain Ischemia/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca**or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	Ischemic Attack, Transient/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	exp Aortic Aneurysm/
9.	Aneurysm, Ruptured/
10.	Aortic Rupture/
11.	((aortic or aorta) adj2 (aneurysm* or rupture* or dissection* or transection* or tear*)).ti,ab.
12.	or/8-11
13.	7 or 12
14.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw,kf.
15.	hypertension/

16.	essential hypertension/
17.	(antihypertens* or hypertens*).tw,kf.
18.	exp blood pressure/
19.	(blood pressure or bloodpressure).tw,kf.
20.	or/15-19
21.	13 and 14 and 20
22.	letter/
23.	editorial/
24.	news/
25.	exp historical article/
26.	Anecdotes as Topic/
27.	comment/
28.	case report/
29.	(letter or comment*).ti.
30.	or/22-29
31.	randomized controlled trial/ or random*.ti,ab.
32.	30 not 31
33.	animals/ not humans/
34.	exp Animals, Laboratory/
35.	exp Animal Experimentation/
36.	exp Models, Animal/
37.	exp Rodentia/
38.	(rat or rats or mouse or mice or rodent*).ti.
39.	or/32-38
40.	21 not 39
41.	limit 40 to English language
42.	randomized controlled trial.pt.
43.	controlled clinical trial.pt.
44.	randomi#ed.ab.
45.	placebo.ab.
46.	randomly.ab.
47.	clinical trials as topic.sh.
48.	trial.ti.
49.	or/42-48
50.	Meta-Analysis/
51.	Meta-Analysis as Topic/
52.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
53.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
54.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56.	(search* adj4 literature).ab.
57.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
58.	cochrane.jw.
59.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
60.	or/50-59

61.	41 and (49 or 60)

Embase (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca**or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	*Transient ischemic attack/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	exp Aortic Aneurysm/
9.	exp Aneurysm, Rupture/
10.	Aortic Rupture/
11.	((aortic or aorta) adj2 (aneurysm* or rupture* or dissection* or transection* or tear*)).ti,ab.
12.	or/8-11
13.	7 or 12
14.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw.
15.	hypertension/
16.	(antihypertens* or hypertens*).tw.
17.	exp blood pressure/
18.	(blood pressure or bloodpressure).mp.
19.	or/15-18
20.	13 and 14 and 19
21.	letter.pt. or letter/
22.	note.pt.
23.	editorial.pt.
24.	case report/ or case study/
25.	(letter or comment*).ti.
26.	(conference abstract or conference paper).pt.
27.	or/21-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animal/ not human/
31.	nonhuman/
32.	exp Animal Experiment/
33.	exp Experimental Animal/
34.	animal model/
35.	exp Rodent/
36.	(rat or rats or mouse or mice or rodent*).ti.
37.	or/29-36

38.	20 not 37
39.	limit 38 to English language
40.	random*.ti,ab.
41.	factorial*.ti,ab.
42.	(crossover* or cross over*).ti,ab.
43.	((doubl* or singl*) adj blind*).ti,ab.
44.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
45.	crossover procedure/
46.	single blind procedure/
47.	randomized controlled trial/
48.	double blind procedure/
49.	or/40-48
50.	systematic review/
51.	Meta-Analysis/
52.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
53.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
54.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56.	(search* adj4 literature).ab.
57.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
58.	cochrane.jw.
59.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
60.	or/50-59
61.	39 and (49 or 60)

Cochrane (Wiley) search terms

#1.	(mini or minor or mild or acute) near/2 (stroke or strokes):ti,ab
#2.	MeSH descriptor: [Brain Ischemia] explode all trees
#3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca**or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#4.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#5.	(isch?emi* near/2 attack*):ti,ab
#6.	TIA*:ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Aortic Aneurysm] explode all trees
#9.	MeSH descriptor: [Aneurysm, Ruptured] explode all trees
#10.	MeSH descriptor: [Aortic Rupture] explode all trees
#11.	(or #8-#10)
#12.	#7 or #11
#13.	((goal* or intensive* or strict* or target* or tight* or optimum or optimal) near/6 (antihypertensive* or anti hypertensive* or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)):ti,ab

#14.	MeSH descriptor: [Hypertension] explode all trees
#15.	MeSH descriptor: [Essential Hypertension] explode all trees
#16.	(antihypertens* or hypertens*):ti,ab
#17.	MeSH descriptor: [Blood Pressure] explode all trees
#18.	(blood pressure or bloodpressure):ti,ab
#19.	(or #13-#18)
#20.	#12 and #19
#21.	conference:pt or (clinicaltrials or trialsearch):so
#22.	#20 not #21

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 10: Health economics search summary

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 2014 – 18 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1946 – 18 June 2021	
Embase (OVID)	Health Economics 2014 – 18 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 18 June 2021	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception – 31 March 2015	
Health Technology Assessment Database (HTA)	Inception – 31 March 2018	

Database	Dates searched	Search filters and limits applied
(Centre for Research and Dissemination – CRD)		
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 18 June 2021	English language

Medline (Ovid) search terms

1.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw,kf.
2.	hypertension/
3.	essential hypertension/
4.	(antihypertens* or hypertens*).tw,kf.
5.	exp blood pressure/
6.	(blood pressure or bloodpressure).tw,kf.
7.	or/2-6
8.	1 and 7
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice or rodent*).ti.
26.	or/19-25
27.	8 not 26
28.	limit 27 to English language
29.	economics/
30.	value of life/
31.	exp "costs and cost analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, medical/
34.	Economics, nursing/
35.	economics, pharmaceutical/

36.	exp "Fees and Charges"/
37.	exp budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	28 and 45
47.	quality-adjusted life years/
48.	sickness impact profile/
49.	(quality adj2 (wellbeing or well being)).ti,ab.
50.	sickness impact profile.ti,ab.
51.	disability adjusted life.ti,ab.
52.	(qal* or qtime* or qwb* or daly*).ti,ab.
53.	(euroqol* or eq5d* or eq 5*).ti,ab.
54.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
55.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
56.	(hui or hui1 or hui2 or hui3).ti,ab.
57.	(health* year* equivalent* or hye or hyes).ti,ab.
58.	discrete choice*.ti,ab.
59.	rosser.ti,ab.
60.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
61.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
62.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
63.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
64.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
65.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
66.	or/47-66
67.	28 and 66
68.	46 or 67

Embase (Ovid) search terms

1.	exp cardiovascular disease/
2.	((heart or myocardial) adj5 (attack* or disease* or infarc*)).tw.
3.	(coronary adj5 (disease* or syndrome*)).tw.
4.	((cardiovascular or peripheral or vascular) adj5 disease*).tw.
5.	atrial fibril*.tw.
6.	((cardiac or heart) adj failure).tw.
7.	angina*.tw.
8.	exp ischemia/
9.	(ischaemi* or ischemi*).tw.
10.	exp stroke/
11.	(CVA or poststroke or post stroke or stroke or strokes).tw.

12.	apoplexy.tw.
13.	cerebrovascul*.tw.
14.	cerebral vascular.tw.
15.	((brain* or cerebral* or lacunar) adj2 (accident* or infarct*)).tw.
16.	or/1-15
17.	((goal? or intensive* or strict* or target* or tight* or optimum or optimal) adj6 (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)).tw.
18.	hypertension/
19.	(antihypertens* or hypertens*).tw.
20.	exp blood pressure/
21.	(blood pressure or bloodpressure).mp.
22.	or/18-21
23.	16 and 17 and 22
24.	letter.pt. or letter/
25.	note.pt.
26.	editorial.pt.
27.	case report/ or case study/
28.	(letter or comment*).ti.
29.	(conference abstract or conference paper).pt.
30.	or/24-29
31.	randomized controlled trial/ or random*.ti,ab.
32.	30 not 31
33.	animal/ not human/
34.	nonhuman/
35.	exp Animal Experiment/
36.	exp Experimental Animal/
37.	animal model/
38.	exp Rodent/
39.	(rat or rats or mouse or mice or rodent*).ti.
40.	or/32-39
41.	23 not 40
42.	limit 41 to English language
43.	health economics/
44.	exp economic evaluation/
45.	exp health care cost/
46.	exp fee/
47.	budget/
48.	funding/
49.	budget*.ti,ab.
50.	cost*.ti.
51.	(economic* or pharmaco?economic*).ti.
52.	(price* or pricing*).ti,ab.
53.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
54.	(financ* or fee or fees).ti,ab.
55.	(value adj2 (money or monetary)).ti,ab.
56.	or/43-55

57.	42 and 56
58.	quality-adjusted life years/
59.	"quality of life index"/
60.	short form 12/ or short form 20/ or short form 36/ or short form 8/
61.	sickness impact profile/
62.	(quality adj2 (wellbeing or well being)).ti,ab.
63.	sickness impact profile.ti,ab.
64.	disability adjusted life.ti,ab.
65.	(qal* or qtime* or qwb* or daly*).ti,ab.
66.	(euroqol* or eq5d* or eq 5*).ti,ab.
67.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
68.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
69.	(hui or hui1 or hui2 or hui3).ti,ab.
70.	(health* year* equivalent* or hye or hyes).ti,ab.
71.	discrete choice*.ti,ab.
72.	rosser.ti,ab.
73.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
74.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
75.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
76.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
77.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
78.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
79.	or/58-78
80.	42 and 79
81.	57 or 80

NHS EED and HTA (CRD) search terms

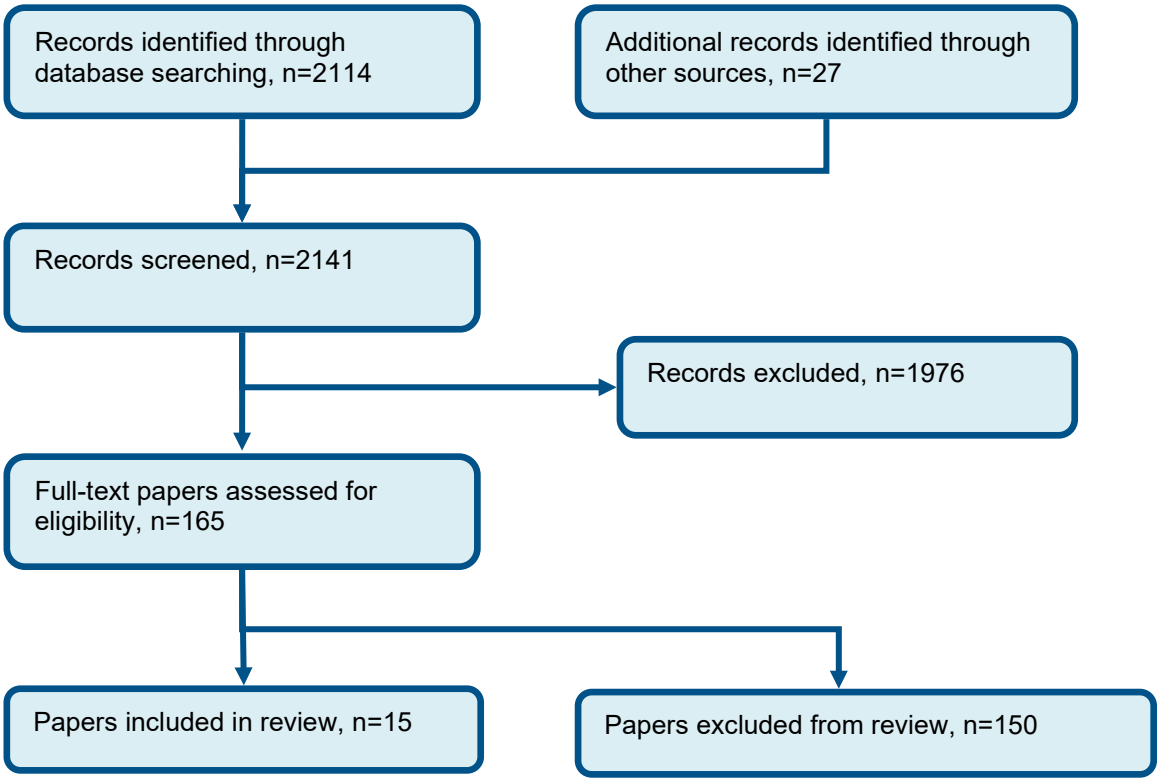
#1.	(goal? or intensive* or strict* or target* or tight* or optimum or optimal) AND (antihypertensive? or anti hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat*)
#2.	MeSH DESCRIPTOR Hypertension
#3.	MeSH DESCRIPTOR Essential Hypertension EXPLODE ALL TREES
#4.	(antihypertens* or hypertens*)
#5.	MeSH DESCRIPTOR blood pressure EXPLODE ALL TREES
#6.	(blood pressure or bloodpressure)
#7.	#2 OR #3 OR #4 OR #5 OR #6
#8.	#1 AND #7

INAHTA search terms

1.	((antihypertens* or hypertens* or blood pressure or bloodpressure)) OR ("Blood Pressure"[mhe]) OR ("Hypertension"[mhe])

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of blood pressure targets



Appendix D – Effectiveness evidence

Benavente, 2013

Bibliographic Reference	Benavente, O. R.; Coffey, C. S.; Conwit, R.; Hart, R. G.; McClure, L. A.; Pearce, L. A.; Pergola, P. E.; Szychowski, J. M.; Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial; Lancet; 2013; vol. 382 (no. 9891); 507-15

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Benavente 2011[6]
Trial name / registration number	SPS3
Study type	Randomised controlled trial (RCT)
Study location	North America, Latin America, Spain
Study setting	Clinical centres

Study dates	March, 2003 - April, 2011
Sources of funding	National Institutes of Health-National Institute of Neurological Disorders and Stroke (NIH-NINDS)
Inclusion criteria	1. Aged 30 years or older 2. Normotensive or hypertensive 3. A recent history of (within 180 days), symptomatic, MRI-confirmed lacunar stroke without surgically amenable ipsilateral carotid artery stenosis or high-risk cardioembolic sources
Exclusion criteria	1. Disabling stroke (modified Rankin score of 4 or higher) 2. Previous intracranial haemorrhage from non-traumatic causes 3. Cortical ischaemic stroke.
Recruitment / selection of participants	Not stated
Population subgroups	1. Age (< 65 vs ≥ 65 years) 2. Race (Hispanic, white, black, other/mixed) 3. Severity of hypertension (Normotensive, baseline SBP < median, baseline SBP ≥ median)
Intervention(s)	Target SBP less than 130 mm Hg. • Participants were randomised at least 2 weeks after the index stroke. • Baseline hypertensive status was determined by measurement of blood pressure taken at two consecutive visits before randomisation. • Patients taking medications to control blood pressure were allowed to continue doing so. • Blood pressure was measured three times at every visit and the average measurement was used to decide hypertensive status.

	• All study sites were provided with automated Colin Press-Mate BP-8800C sphygmomanometers • Blood pressure management was overseen at each site by a physician with special expertise in blood-pressure control. • The algorithm advocates titration of dose, as well as the addition of agents, using a step-wise approach, monitoring carefully for specific side effects of agents or due to lowering of blood pressure. • Patients are seen at least monthly for adjustment of antihypertensive medications to achieve the assigned target blood pressure. Once the systolic blood pressure is in the assigned target range at two consecutive visits, the participant continues with quarterly follow-ups.
Comparator	Target SBP 130–149 mm Hg • Blood pressure management as above If SBP dropped below the lower limit of the target range, patients on antihypertensive medications stopped taking them or had the doses reduced.
Number of participants	3020
Duration of follow-up	3.7 years
Indirectness	BP targets used Intensive <130mmHg Standard 130-149mmHg Slightly different in protocol Intensive ≤130 mm Hg, Standard ≤140mmHg
Additional comments	All analyses were based on the intention-to-treat principle Treatment algorithm for titration of dose and the addition of agents, using a step-wise approach in both groups.

Study arms

Intensive BP control (N = 1501)

SBP < 130mmHg

Standard BP control (N = 1519)

130-149 mmHg

Characteristics

Study-level characteristics

Characteristic	**Study (N = 3020)**
Time from last CV event to randomisation (median days) Nominal	62

Arm-level characteristics

Characteristic	**Intensive BP control (N = 1501)**	**Standard BP control (N = 1519)**
Number of patients reaching BP target (n (%)) Sample size	n = 976 ; % = 65	n = 1139 ; % = 75

Characteristic	Intensive BP control (N = 1501)	Standard BP control (N = 1519)
Age (years) Mean (SD)	63 (10.7)	63 (10.8)
Male (n (%)) Sample size	n = 912 ; % = 61	n = 990 ; % = 65
White Sample size	n = 778 ; % = 52	n = 760 ; % = 50
Hispanic Sample size	n = 448 ; % = 30	n = 468 ; % = 31
Black Sample size	n = 241 ; % = 16	n = 251 ; % = 17
Other Sample size	n = 34 ; % = 2	n = 40 ; % = 3
Systolic blood pressure Mean (SD)	142 (19)	144 (19)
Diastolic blood pressure Mean (SD)	78 (10)	79 (11)
Diabetes mellitus (n (%)) Sample size	n = 553 ; % = 37	n = 553 ; % = 36

Characteristic	Intensive BP control (N = 1501)	Standard BP control (N = 1519)
Ischemic heart disease Sample size	n = 144 ; % = 10	n = 173 ; % = 11
Previous Clinical Stroke or TIA Sample size	n = 237 ; % = 16	n = 211 ; % = 14
Ischemic Stroke Qualifying event Sample size	n = 1473 ; % = 98	n = 1506 ; % = 99
TIA Qualifying event Sample size	n = 28 ; % = 2	n = 13 ; % = 1
Number of antihypertensive medications at study entry Mean (SD)	1.7 (1.2)	1.7 (1.2)
Anti-hypertensives at 1 year		
Thiazides Sample size	n = 774 ; % = 58	n = 576 ; % = 43
ACE inhibitor/ARB Sample size	n = 1064 ; % = 80	n = 835 ; % = 63
Calcium channel blockers Sample size	n = 571 ; % = 43	n = 398 ; % = 30

Characteristic	Intensive BP control (N = 1501)	Standard BP control (N = 1519)
Beta blockers Sample size	n = 408 ; % = 31	n = 333 ; % = 25
Other Sample size	n = 146 ; % = 11	n = 117 ; % = 9
Final SBP values (mmHg) Nominal (mean; 95% CI)	127 (95% CI 126–128)	138 (95% CI 137–139)

Outcomes

Study timepoints

- 3.7 year (Mean follow up time period)

Results - hazard ratio

Outcome	Intensive BP control vs Standard BP control, 3.7 year, N2 = 1501, N1 = 1519
All-cause mortality (ln) Secondary outcome Hazard ratio/95% CI	1.03 (0.79 to 1.35)
All Stroke Hazard ratio/95% CI	0.81 (0.64 to 1.03)

Outcome	Intensive BP control vs Standard BP control, 3.7 year, N2 = 1501, N1 = 1519
Myocardial infarction (ln) Secondary outcome Hazard ratio/95% CI	0.88 (0.56 to 1.39)

Results - raw data

Outcome	Intensive BP control, 3.7 year, N = 1501	Standard BP control, 3.7 year, N = 1519
All-cause mortality (Number of patients with an event) No of events	n = 106 ; % = 7	n = 101 ; % = 6.6
Stroke (Number of patients with an event) No of events	n = 125 ; % = 8.3	n = 152 ; % = 10
Myocardial infarction (Number of patients with an event) No of events	n = 36 ; % = 2.4	n = 40 ; % = 2.6
Number of drugs at end of trial Mean (SD)	2.4 (1.3)	1.8 (1.4)

All-cause mortality - Polarity - Lower values are better

Stroke - Polarity - Lower values are better

Myocardial infarction - Polarity - Lower values are better

Number of drugs at end of trial - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality- 3.7 years

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information provided)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirect BP target threshold)*

All Stroke - 3.7 years

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information provided)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirect BP target threshold)*

Myocardial infarction - 3.7 years

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Limited information provided)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data comparable to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirect BP target threshold)*

Number of drugs at end of trial- 3.7 years

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information provided)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(patients and caregivers not blinded to allocation)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirect BP target threshold)*

Kitagawa, 2019

Bibliographic Reference	Kitagawa, K.; Yamamoto, Y.; Arima, H.; Maeda, T.; Sunami, N.; Kanzawa, T.; Eguchi, K.; Kamiyama, K.; Minematsu, K.; Ueda, S.; Rakugi, H.; Ohya, Y.; Kohro, T.; Yonemoto, K.; Okada, Y.; Higaki, J.; Tanahashi, N.; Kimura, G.; Umemura, S.; Matsumoto, M.; Shimamoto, K.; Ito, S.; Saruta, T.; Shimada, K.; Recurrent Stroke Prevention Clinical Outcome Study, Group; Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis; JAMA Neurology; 2019; vol. 76 (no. 11); 1309-1318

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None
Trial name / registration number	RESPECT
Study type	Randomised controlled trial (RCT)
Study location	Japan
Study setting	Hospitals in Japan
Study dates	September 2010 - December 2018 (including data analysis); enrolment: until December 2015.
Sources of funding	SPONSOR: • MARCK and Co. • Bristol-Myers Squibb Company • TOWA PHARMACEUTICAL CO., LTD • OMRON Corporation
Inclusion criteria	1. Age 50 to 85 years

	2. Independent ambulation 3. Systolic BP of 130 to 180 mm Hg or diastolic BP of 80 to 110 mm Hg 4. On a regimen of 0 to 3 antihypertensive medications 5. A history of stroke with onset 30 days to 3 years previously (evidence of an acute disturbance of focal neurological functions, with symptoms lasting more than 24 hours, and symptomatic ischemic stroke or intracerebral hemorrhage confirmed by magnetic resonance imaging or computed tomography) 6. Drug adherence ≥80% during the screening period.
Exclusion criteria	1. Women who are pregnant, trying to become pregnant, or are breastfeeding 2. Secondary hypertension 3. Severe hypertension (grade III or greater) with baseline SBP more than 180 mmHg or DBP more than 110 mmHg) 4. Onset of myocardial infarction or undergoing angioplasty that occurred within 3 months prior to consent 5. Current or previous heart failure with NYHA classification class III or more, or 318 EF ≤35% 6. Severe bilateral carotid stenosis or major cerebral artery occlusion 7. Severe paralysis due to stroke (modified Rankin scale more than 4) 8. Current renal dysfunction (serum creatinine more than 2.0 mg/dL within 1 year prior to consent) 9. Current hepatic dysfunction with AST (GOT) or ALT (GPT) value more than 100 IU/mL within 1 year prior to consent 10. Essential hypertension treated with four or more antihypertensive drugs

	11. Hypersensitivity to angiotensin II receptor blockers, thiazide, sulfonamide derivative, dihydropyridine drugs or spironolactone. 12. Major surgery planned during the study period 13. Participants who participated in other clinical studies within the last 30 days 14. Current malignancy (previous malignancy within 5 years after the end of 331 treatment) excluding skin squamous cell carcinoma 15. Current or previous subarachnoid hemorrhage 16. Definitive dementia (based on a clinical diagnosis) 17. Patients who have difficulty in signing consent or who do not agree to the provided consent 18. Patients who are judged to be unsuitable for participating the study by the primary investigator or sub-investigator.
Recruitment / selection of participants	Not stated
Population subgroups	1. Age (<70 vs ≥70 years) 2. Chronic kidney disease (presence or absence)
Intervention(s)	BP target less than 120/80 mm Hg. • The intensive treatment group received stepwise multidrug therapy starting with an ARB with a BP target less than 120/80 mm Hg. • The study used a combination drug of losartan potassium or other angiotensin II receptor blockers and hydrochlorothiazide, amlodipine besylate, and spironolactone to control BP. • To achieve the target BP, patients received stepwise treatments orally every 4 weeks for 24 weeks at maximum during the titration period

	• Clinic blood pressure monitoring was in line with guidelines: properly calibrated mercury/aneroid or electronic manometer seated after rest with measurement taken at least twice, allowing a 1 to 2-minute interval. If the blood pressure levels from these two measurements were extremely different from each other, a third blood pressure reading was taken. The mean of 2 stable values was used. The use of an automatic cuff winding device in the waiting room allowed if carefully supervised to prevent errors.
Comparator	BP control groups with targets of less than 140/90 mm Hg (the standard treatment group [n = 640]) The standard treatment group received the same blood pressure measurement and stepwise therapy starting with an ARB with BP targets less than 140/90 mm Hg or less than 130/80 mm Hg for patients who have diabetes, chronic kidney disease, or a history of MI. However, down titration of medication was recommended for those with DM, CKD, prior MI (if SBP ≤120 at 1 visit or ≤125 at 2 consecutive visits) or stroke risk factors (if SBP ≤130 at 1 visit or ≤135 at 2 consecutive visits).
Number of participants	1263 Trial enrolment stopped early, before reaching the planned sample size, because of slow recruitment and funding cessation.
Duration of follow-up	3.5 years -
Indirectness	None
Additional comments	1. The study used a combination drug of losartan potassium or other angiotensin II receptor blockers and hydrochlorothiazide, amlodipine besylate, and spironolactone to control BP. To achieve the target BP, patients received stepwise treatments orally every 4 weeks for 24 weeks at maximum during the titration period 2. All patients except for those who immediately withdrew their consent and those without any information after randomization were included in the analysis. All analyses were based on the intent-to-treat principle.

	3. Cumulative incidence was estimated using the Kaplan-Meier method and compared using a log-rank test between randomized groups. 4. The effects of strict BP control on outcomes were calculated using univariable Cox proportional hazards models and are reported as hazard ratios (HRs) and 95% CIs.

Study arms

Intensive BP control (N = 633)

SBP/DBP < 120/80mm Hg

Standard BP control (N = 630)

SBP/DBP < 140/90mmHg

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1263)**
Time from last CV event to randomisation Custom value	More than 1 month

Arm-level characteristics

Characteristic	Intensive BP control (N = 633)	Standard BP control (N = 630)
Number of patients reaching BP target Sample size	n = 197 ; % = 32	n = 374 ; % = 61.7
Age (Mean (SD), y) Mean (SD)	67.2 (8.8)	67.3 (8.8)
Male (n (%)) Sample size	n = 449 ; % = 70.9	n = 428 ; % = 67.9
Systolic blood pressure Mean (SD)	145.1 (12.4)	145.7 (12.9)
Diastolic blood pressure Mean (SD)	83.6 (10.7)	83.7 (10.4)
Diabetes (n (%)) Sample size	n = 142 ; % = 22.4	n = 154 ; % = 24.4
Coronary heart disease Sample size	n = 15 ; % = 2.4	n = 17 ; % = 2.7
Stroke/TIA Sample size	n = 94 ; % = 14.8	n = 99 ; % = 15.7
Ischemic Stroke Sample size	n = 532 ; % = 84	n = 542 ; % = 86

Characteristic	Intensive BP control (N = 633)	Standard BP control (N = 630)
Intracerebral Haemorrhage Sample size	n = 101 ; % = 16	n = 88 ; % = 14
Chronic kidney disease (n (%)) Sample size	n = 36 ; % = 5.7	n = 27 ; % = 4.3
Final BP values Custom value	126.7/74.4	133.2/77.7
Number of antihypertensive medications at study entry Mean	1.5	1.4

Outcomes

Study timepoints

- 3.9 year (Mean follow up time period)

Number of drugs at trial end (Mean) Custom value	2.8	1.6

Results – hazard ratios

Outcome	Intensive BP control vs Standard BP control, 3.9 year, N2 = 633, N1 = 630
All cause death	0.8 (0.49 to 1.29)

Outcome	Intensive BP control vs Standard BP control, 3.9 year, N2 = 633, N1 = 630
Hazard ratio/95% CI	
Stroke HR Hazard ratio/95% CI	0.73 (0.49 to 1.11)
Myocardial infarction Hazard ratio/95% CI	1.23 (0.33 to 4.59)

Results – raw data

Outcome	Intensive BP control, 3.9 year, N = 633	Standard BP control, 3.9 year, N = 630
All cause death Secondary outcome No of events	n = 30 ; % = 1.22	n = 37 ; % = 1.52
Stroke Ischemic stroke and intracerebral haemorrhage No of events	n = 39 ; % = 1.65	n = 52 ; % = 2.26
Myocardial infarction Secondary outcome No of events	n = 5 ; % = 0.2	n = 4 ; % = 0.17
New-onset or worsening heart failure No of events	n = 5 ; % = 0.79	n = 3 ; % = 0.47
Coronary intervention or surgery	n = 10 ; % = 1.58	n = 11 ; % = 1.74

Outcome	Intensive BP control, 3.9 year, N = 633	Standard BP control, 3.9 year, N = 630
No of events		
Worsening renal function No of events	n = 6 ; % = 0.95	n = 1 ; % = 0.16
Bone fracture No of events	n = 13 ; % = 2.05	n = 17 ; % = 2.7

All-cause mortality - Polarity - Lower values are better

Stroke - Polarity - Lower values are better

Myocardial infarction - Polarity - Lower values are better

New-onset or worsening heart failure - Polarity - Lower values are better

Coronary intervention or surgery - Polarity - Lower values are better

Worsening renal function - Polarity - Lower values are better

Bone fracture - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All cause mortality - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Stroke - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Myocardial Infarction - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data comparable to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

New onset or worsening heart failure - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data comparable to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Coronary intervention surgery - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Worsening renal function - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data comparable to event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Bone fracture - 3.9 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold comparison)*

Mant, 2016

Bibliographic Reference	Mant, J.; McManus, R. J.; Roalfe, A.; Fletcher, K.; Taylor, C. J.; Martin, U.; Virdee, S.; Greenfield, S.; Hobbs, F. D.; Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke--Blood Pressure) randomised controlled trial; Bmj; 2016; vol. 352; i708

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Fletcher 2010[13] Saiz 2020[23]
Trial name / registration number	PAST-BP
Study type	Randomised controlled trial (RCT)
Study location	England
Study setting	General practices (Primary care)
Study dates	2009 - 2011
Sources of funding	Funded by the National Institute for Health Research (NIHR; Stroke Prevention in Primary Care, Programme Grant for Applied Research, RP-PG-0606- 1153) and by an NIHR Professorship (RJMcM).

Inclusion criteria	Patients were considered for inclusion if they were on the practice's TIA/stroke register
Exclusion criteria	1. Baseline systolic blood pressure was less than 125 mm Hg 2. Already taking three or more antihypertensive agents 3. Had a greater than 20 mm Hg postural change in systolic blood pressure on standing 4. Already being treated to a 130 mm Hg systolic blood pressure target 5. Unable to provide informed consent 6. Insufficient corroborative evidence that they had had a stroke or TIA
Recruitment / selection of participants	Eligible patients were identified from general practices from the Central England Primary Care Research Network and from the Midlands Research Practice Consortium (MidReC). Each practice will run a search of their clinical computer system to identify all patients on the stroke/TIA register.). Patients with no clear exclusion criteria at this stage were sent a letter inviting them to attend a study baseline clinic appointment.
Population subgroups	Age (<80 vs ≥80 years)
Intervention(s)	Patients randomised to the intensive arm were given a target systolic blood pressure of below 130 mm Hg or a target reduction of 10 mm Hg if their baseline blood pressure was between 125 and 140 mm Hg. • The management of blood pressure was the same in both groups and was carried out by a practice nurse (to monitor blood pressure) and a general practitioner (responsible for modifying blood pressure treatment). • Everyone in the intensive arm and those patients in the standard arm whose blood pressure was ≥140 mm Hg) had their antihypertensive treatment reviewed by their general practitioner. • The protocol required no formal down-titration of treatment if blood pressure was below target • Blood pressure was measured using a British Hypertension Society validated automated electronic monitor supplied and validated for the study. • Blood pressure was measured in a standardised way by a practice nurse. The patient was seated for 5 minutes and then 6 measurements taken at minute intervals. The second and third measurements were averaged to give the reading.

	• • All patients in the intensive target arm will have their BP lowering therapy intensified at trial entry since the target will be automatically below their baseline BP
Comparator	• The target in the standard arm was less than 140 mm Hg, irrespective of baseline blood pressure. • only those patients in the standard arm whose BP is above 140/90 mmHg will have their therapy intensified at the outset.
Number of participants	529
Duration of follow-up	12 months
Indirectness	SBP target slightly different from protocol (<130 mm Hg) for Intensive treatment Population indirectness: not all hypertensive (48% had SBP<140 at baseline)
Additional comments	Patients were censored at the time of the first event relevant to that analysis. Thus, if a patient had more than one emergency hospital admission, only the first one would be counted. ITT not stated.

Study arms

Intensive SBP target (N = 266)

<130 mm Hg or a 10 mm Hg reduction if baseline pressure was <140mm Hg

Standard SBP target (N = 263)

<80 mm Hg

Arm-level characteristics

Characteristic	Intensive SBP target (N = 266)	Standard SBP target (N = 263)
Number of patients reaching BP targets (n (%)) Sample size	n = 93 ; % = 51	n = 161 ; % = 82
Age (years) Mean (SD)	71.9 (9.1)	71.7 (9.4)
Male (n (%)) Sample size	n = 157 ; % = 59	n = 156 ; % = 59
Systolic blood pressure Mean (SD)	142.9 (14)	142.2 (13.4)
SBP <140 mmHg Mean (SD)	128 (48)	129 (49)
SBP >140 mm Hg Mean (SD)	138 (52)	134 (51)
Diastolic blood pressure Mean (SD)	79.9 (10)	80.4 (9.8)
White ethnicity (n (%)) Sample size	n = 260 ; % = 98	n = 259 ; % = 98

Characteristic	Intensive SBP target (N = 266)	Standard SBP target (N = 263)
Diabetes mellitus (n (%)) Sample size	n = 26 ; % = 10	n = 25 ; % = 10
Coronary heart disease Sample size	n = 41 ; % = 15	n = 46 ; % = 17
Heart failure Sample size	n = 2 ; % = 1	n = 7 ; % = 3
Peripheral vascular disease Sample size	n = 11 ; % = 4	n = 11 ; % = 4
Stroke Sample size	n = 130 ; % = 49	n = 122 ; % = 46
TIA only Sample size	n = 135 ; % = 51	n = 141 ; % = 54
Number of antihypertensive medications at study entry Mean (SD)	1.0 (0.8)	1.1 (0.8)

Outcomes

Study timepoints

- 12 month

Results - Hazard Ratio

Outcome	**Intensive SBP target vs Standard SBP target, 12 month, N2 = 266, N1 = 263**
Risk of emergency admission Hazard ratio/95% CI	1.56 (0.84 to 2.93)

Results – raw data

Outcome	**Intensive SBP target, 12 month, N = 266**	**Standard SBP target, 12 month, N = 263**
Mortality No of events	n = 2 ; % = 0.75	n = 1 ; % = 0.3
Stroke No of events	n = 0 ; % = 0	n = 3 ; % = 1.1
Myocardial infarction No of events	n = 1 ; % = 0.3	n = 1 ; % = 0.3
Drugs at end of trial (mean per person) Mean (SD)	2.1 (1.52)	1.9 (1.52)
GP visits (median) p<0.001 Custom value	2	1
Practice nurse visits (median) p=0.002 Custom value	3	2

Outcome	Intensive SBP target, 12 month, N = 266	Standard SBP target, 12 month, N = 263
Risk of emergency admission (Percent per year) Nominal	12.8	7.8
Falls Hospital admission for fall No of events	n = 2 ; % = 0.75	n = 2 ; % = 0.76

Mortality - Polarity - Lower values are better

Stroke - Polarity - Lower values are better

Myocardial infarction - Polarity - Lower values are better

Drugs at end of trial - Polarity - Lower values are better

GP visits - Polarity - Lower values are better

Practice nurse visits - Polarity - Lower values are better

Risk of emergency admission - Polarity - Lower values are better

Falls - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Mortality - 12 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target thresholds and population indirectness)*

Stroke - 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP targets thresholds and population indirectness)*

Myocardial Infarction - 12 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold and population indirectness)*

Drugs at end of trial - 12 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(unblinded)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a* high *proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(8% differential proportion missing between groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold and population indirectness)*

GP visits - 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(unblinded)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a* high *proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(8% differential proportion missing between groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold and population indirectness)*

Practice nurse visits - 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(unblinded)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(8% differential proportion missing between groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target thresholdand population indirectness)*

Risk of emergency admission - 12 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP targets threshold and population indirectness)*

Falls - 12 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(a high proportion stopped treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP target threshold and population indirectness)*

Markus, 2021

Bibliographic Reference	Markus, H. S.; Egle, M.; Croall, I. D.; Sari, H.; Khan, U.; Hassan, A.; Harkness, K.; MacKinnon, A.; O'Brien, J. T.; Morris, R. G.; Barrick, T. R.; Blamire, A. M.; Tozer, D. J.; Ford, G. A.; Team, Preserve Study; Team, Preserve Study; PRESERVE: Randomized Trial of Intensive Versus Standard Blood Pressure Control in Small Vessel Disease; Stroke; 2021; trokeaha120032054

Study details

Secondary publication of another included study- see primary study for details	Not stated
Other publications associated with this study included in review	None
Trial name / registration number	PRESERVE
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	University hospitals
Study dates	Not stated
Sources of funding	The study was funded by a joint British heart Foundation the Stroke Association programme grant (TSA BHF 2010/01)

Inclusion criteria	• Clinical lacunar stroke with an anatomically corresponding lacunar infarct on MRI, in addition to confluent WMH graded >2 on the Fazekas scale. • Ages > 40 years • Hypertensive • SBP >140mmHg or 125-140mmHg on antihypertensive medication
Exclusion criteria	• Single gene disorder causing small vessel disease • Cause of stroke other than small vessel disease • Diagnosis of dementia on DSM IV criteria
Recruitment / selection of participants	Not stated
Population subgroups	None
Intervention(s)	Intensive systolic BP target <125mmHg • BP lowering treatment increased at baseline assessment and reviewed by telephone at two weekly intervals. If average BP at any follow-up is >125 mmHg treatment will be increased until target systolic BP of <125 mm Hg is achieved (average of 2nd and 3rd of three seated BP readings), or symptoms of hypotension prevent treatment being intensified. If dose of an existing drug is instituted this can be done over the telephone but if a new agent is required the patient will attend for the prescription. • All subjects were seen 1,3,6,12,18,24 months for clinical assessment and BP monitoring. • Additional clinic or telephone BP check ups were performed as necessary. • During clinic visits, BP was measured in sitting position 3x following a 10 minute rest period in quiet room • Recorded BP was mean of second and third measures • Both groups also given home blood pressure monitors and asked to perform daily blood pressure readings for at least 3 days prior to each pre-arranged telephone follow-up. • Treatment algorithms consistent with BHS/NICE • Down-titration not mentioned

Comparator	Standard systolic BP target 130-140mmHg Treatment unchanged at study entry. Contacted for two weekly intervals for the first month and then seen for regular follow-up. At follow-up if average systolic BP is above 140 mmHg treatment will be increased until target systolic BP of <140mmHg or symptoms of hypotension prevent treatment being intensified.
Number of participants	111
Duration of follow-up	24 months
Indirectness	BP targets used intensive SBP<125mmHg vs standard 130-140mmHg are slightly different from protocol.
Additional comments	Primary analysis was ITT.

Study arms

Intensive BP control (N = 55)

< 125mm Hg

Standard BP control (N = 56)

130-140 mmHg

Characteristics

Study-level characteristics

Characteristic	Study (N = 81)
Time from last CV event to randomisation (Months) Nominal	3

Arm-level characteristics (only reported for those with complete DTI data)

Characteristic	Intensive BP control (N = 42)	Standard BP control (N = 39)
Age (years) Mean (SD)	68.13 (8.66)	69.58 (9.35)
Male (n (%)) Sample size	n = 25 ; % = 59	n = 23 ; % = 59
Systolic BP (mmHg) Mean (SD)	149.29 (14.8)	147.77 (11.53)
Diabetes (n (%)) Sample size	n = 1 ; % = 2	n = 1 ; % = 3
Myocardial infarction, CABG or coronary angioplasty (n (%)) Sample size	n = 2 ; % = 5	n = 2 ; % = 5
Peripheral vascular disease (n (%)) Sample size	n = 1 ; % = 2	n = 1 ; % = 3

Characteristic	Intensive BP control (N = 42)	Standard BP control (N = 39)
Number of patients reaching BP targets (n (%)) Sample size	n = 26 ; % = 32	n = 33 ; % = 40.7
Final BP values (mmHg) SBP Nominal	127	140

Outcomes

Study timepoints

- 24 month

Results – raw data

Outcome	Intensive BP control, 24 month, N = 55	Standard BP control, 24 month, N = 56
Death (n (%)) No of events	n = 1 ; % = 2.3	n = 2 ; % = 5.1
Stroke (n (%)) No of events	n = 3 ; % = 7.1	n = 3 ; % = 7.6
Acute kidney injury No of events	n = 1 ; % = 2.3	n = 0 ; % = 0

Death - Polarity - Lower values are better

Stroke - Polarity - Lower values are better

Acute kidney injury - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Mortality - 24 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *('indirect BP target threshold comparison)*

Stroke - 24 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *('indirect BP target threshold comparison)*

Acute Kidney Injury - 24 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(proportion of missing data greater than event rate)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *('indirect BP target threshold comparison)*

Saiz, 2020

Bibliographic Reference	Saiz, Lc; Gorricho, J; Garjón, J; Celaya, Mc; Erviti, J; Leache, L; Blood pressure targets for the treatment of people with hypertension and cardiovascular disease; Cochrane Database of Systematic Reviews; 2020; (no. 9)

Study Characteristics

Study design	Systematic review Cochrane review
Study details	Dates searched evidence up to November 2019 Databases searched • Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 6 November 2019). • Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 6 November 2019). • MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 6 November 2019).

	• Embase Ovid (from 1974 onwards) (searched 6 November 2019). • Latin American and Caribbean Health Sciences Literature (LILACS) Bireme (from 1982 onwards) (searched 6 November 2019). • ClinicalTrials.gov (www.clinicaltrials.gov) (searched 6 November 2019). • World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 6 November 2019)
Study and participant inclusion criteria	Included participants • At least 18 years of age • Hypertension documented in a standard way, or had to be receiving treatment for hypertension, with a positive cardiovascular history of myocardial infarction, stroke (not including transient ischaemic attack (TIA)), chronic peripheral vascular occlusive disease, or angina pectoris. Included study types randomized controlled trials (RCTs) with more than 50 participants per group and at least six months' follow-up.
Study and participant exclusion criteria	Excluded participants: Not stated Excluded studies: Trials that used anything other than accepted randomized allocation methods such as alternate allocation, week of presentation, or retrospective controls.
Intervention(s)	Intervention: lower blood pressure treatment target: systolic/ diastolic 135/85 mmHg or less; mean blood pressure (MBP) 102 mmHg or less. Control: standard blood pressure treatment target: systolic/ diastolic 140 to 160/90 to 100 mmHg or less; MBP 107 to 120 mmHg or less.

Outcome(s)	Primary outcomes: • Total mortality. • Total serious adverse events. • Total cardiovascular events including myocardial infarction, stroke, sudden death, hospitalization or death from congestive heart failure, and other significant vascular events such as ruptured aneurysms (excluding angina, TIA, surgical or other procedures, or accelerated hypertension). In practice, this was measured as total number of participants with at least one cardiovascular event, including fatal and non-fatal cardiovascular events. • Cardiovascular mortality Secondary outcomes: • Participant withdrawals due to adverse effects. • SBP and the difference from baseline at one year, or both. • DBP and the difference from baseline at one year, or both. • Proportion of participants reaching the target blood pressure level. • Number of antihypertensive drugs that each participant needed at the end of the study.
Number of studies included in the systematic review	Included six studies • AASK 2002 • ACCORD BP 2010 • HOT 1998 • PAST BP 2016 • SPRINT 2015

	• SPS3 2013
Studies from the systematic review that are relevant for use in the current review	Study 1 ACCORD-BP 2010 Study 2 HOT 1998 Study 3 PAST-BP 2016 Study 4 SPRINT 2015
Original publications associated with studies from the systematic review that are relevant for use in the current review	**ACCORD BP:** Cushman 2010[10], Buse 2007[8] and Cushman 2007[11] **HOT**: Hansson 1998[16] and Hansson 1993[15] **PAST BP**: Mant 2016[19] and Fletcher 2010[13] **SPRINT**: Ambrosius 2014[1] and Wright 2015[25]
Studies from the systematic review that are not relevant for use in the current review	Study 1 AASK 2002 Study 2SPS3 2013

Study arms

Intensive Blood Pressure (N = 5301)

135/85 mmHg or less

Standard Blood Pressure (N = 4183)

140 to 160/90 to 100 mmHg or less

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Mean age	
ACCORD BP (n=1531) Mean (SD)	62 (8)
HOT (n=3232) Mean (SD)	62 (NR)
SPRINT (n=1562) Mean (SD)	70 (9)
% male	

Characteristic	Study (N =)
ACCORD BP (n=1531) Nominal	63
HOT (n=3232) Nominal	53
SPRINT (n=1562) Nominal	76
Baseline SBP	
ACCORD BP (n=1531) Mean (SD)	138 (16)
HOT (n=3232) Mean (SD)	174 (15)
SPRINT (n=1562) Mean (SD)	138 (16)
Baseline DBP	
ACCORD BP (n=1531) Mean (SD)	74 (11)
HOT (n=3232) Mean (SD)	106 (3)

Characteristic	Study (N =)
SPRINT (n=1562) Mean (SD)	74 (12)
Ethnicity - white	
ACCORD BP (n=1531) Nominal	62
HOT (n=3232) Nominal	92
SPRINT (n=1562) Nominal	71
Previous cardiovascular condition - ischaemic heart disease	
ACCORD BP (n=1531) Nominal	86
HOT (n=3232) Nominal	95
SPRINT (n=1562) 100% had IHD or peripheral vascular disease Nominal	NR
Previous cardiovascular condition - stroke	

Characteristic	Study (N =)
ACCORD BP (n=1531) Nominal	20
HOT (n=3232) Nominal	7
SPRINT (n=1562) Nominal	0
Types of drugs at 1 year in ACCORD BP (n=1531)	
Thiazides Nominal	51
ACEIs/ARBs Nominal	84
CCB Nominal	26
BB Nominal	57
Other Nominal	28

Outcomes

Study timepoints

- 4 year (Average follow up period of trials)

Results - raw data for ACCORD BP

Outcome	Intensive Blood Pressure, 4 year, N = 772	Standard Blood Pressure, 4 year, N = 759
All-cause mortality ACCORD BP - 4.7 years No of events	n = 78 ; % = 10.1	n = 64 ; % = 8.4
Cardiovascular events ACCORD BP - 4.7 years No of events	n = 131 ; % = 17	n = 154 ; % = 20.3
Number of antihypertensive drugs needed per participant at the end of study ACCORD BP - 4.7 years Mean (SD)	3.6 (1.3) N=592 for this outcome (not available for all participants)	2.6 (1.2) N=593 for this outcome (not available for all participants)

All-cause mortality - Polarity - Lower values are better

Cardiovascular events - Polarity - Lower values are better

Serious adverse events - Polarity - Lower values are better

Number of antihypertensive drugs needed per participant at the end of study- Polarity - Lower values are better

Results - raw data for HOT

Outcome	Intensive Blood Pressure, 4 year, N = 2168	Standard Blood Pressure, 4 year, N = 1064
All-cause mortality HOT - 3.8 years No of events	n = 127 ; % = 5.9	n = 56 ; % = 5.3
Cardiovascular events HOT - 3.8 years No of events	n = 172 ; % = 7.9	n = 89 ; % = 8.4
Withdrawal due to adverse events HOT - 3.8 years Custom value	5/226 (2.2%)	1/129 (0.78%)
Number of antihypertensive drugs needed per participant at the end of study HOT - 3.8 years Mean (SD)	1.9 (0.79) N=1809 for this outcome (not available for all participants)	1.75 (0.77) N=895 for this outcome (not available for all participants)

All-cause mortality - Polarity - Lower values are better

Cardiovascular events - Polarity - Lower values are better

Serious adverse events - Polarity - Lower values are better

Withdrawal due to adverse events - Polarity - Lower values are better

Number of antihypertensive drugs needed per participant at the end of study- Polarity - Lower values are better

Results - raw data for SPRINT

Outcome	Intensive Blood Pressure, 4 year, N = 779	Standard Blood Pressure, 4 year, N = 783
All-cause mortality SPRINT - median 3.26 years No of events	n = 45 ; % = 5.8	n = 65 ; % = 8.3
Number of antihypertensive drugs needed per participant at the end of study SPRINT - median 3.26 years Mean (SD)	3 (1)	2 (1.1)

All-cause mortality - Polarity - Lower values are better

Number of antihypertensive drugs needed per participant at the end of study- Polarity - Lower values are better

Results - raw data for PAST BP (excluding those with prior TIA)

Outcome	Intensive Blood Pressure, 4 year, N = 154	Standard Blood Pressure, 4 year, N = 141
Withdrawal due to adverse events PAST-BP - 1 year No of events	n = 17 ; % = 11	n = 1 ; % = 0.7

Withdrawal due to adverse events - Polarity - Lower values are better

Note: Outcome not available in full study report

Critical appraisal - ROBIS checklist

All-cause mortality (ACCORD BP)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA)*

Cardiovascular events (ACCORD BP)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low

Section	Question	Answer
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA)*

Number of antihypertensive drugs (ACCORD BP)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Unblinded and data not available for all)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA)*

All-cause mortality (HOT)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low

Section	Question	Answer
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Post-hoc subgroup analysis)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA and indirect BP target threshold)*

Cardiovascular events (HOT)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Post hoc subgroup analysis)*
Overall study ratings	Overall risk of bias	High

Section	Question	Answer
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA and indirect BP target threshold)*

Withdrawal due to adverse events (HOT)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Data only available for some patients based on free text entries to the database and unblinded)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA and indirect BP target threshold)*

Number of antihypertensive drugs (HOT)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Unblinded and data not available for all)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA)*

All-cause mortality (SPRINT)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA and indirect BP target threshold)*

Withdrawal due to adverse events (PAST BP)

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	High *(unblinded)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable *(Definition of CVD excluded TIA and indirect BP target threshold)*

Vlachopoulos, 2019

Bibliographic Reference	Vlachopoulos, C.; Terentes-Printzios, D.; Aznaouridis, K.; Ioakeimidis, N.; Xaplanteris, P.; Lazaros, G.; Tousoulis, D.; Effects of Intensive Blood Pressure Control in Patients with Evident Cardiovascular Disease: An Investigation Using the SPRINT Study Data; Current Vascular Pharmacology; 2019; vol. 17 (no. 3); 298-306

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Ambrosius 2014[1] Saiz 2020[23] Wright 2015[25]
Trial name / registration number	SPRINT
Study type	Randomised controlled trial (RCT)
Study location	United States
Study setting	Clinical sites
Study dates	Not stated

Sources of funding	Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062
Inclusion criteria	• Age of at least 50 years • A systolic blood pressure of 130 to 180 mm Hg • An increased risk of cardiovascular events (Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m2 of body surface area, calculated with the use of the four variable Modification of Diet in Renal Disease equation; a 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older)
Exclusion criteria	Patients with • Diabetes mellitus • Polycystic kidney disease • Screening urine protein level of >1 g/day or equivalent, • Symptomatic heart failure • Ejection fraction <35% • Stroke
Recruitment / selection of participants	Recruitment strategies targeting both existing populations within the clinical practice of the research sites as well as individuals from outside these practice settings will be used to identify potentially eligible participants.
Population subgroups	None
Intervention(s)	• Participants were assigned to a systolic blood-pressure target of less than 120 mm Hg (the intensive-treatment group). • Participants were seen monthly for the first 3 months and every 3 months thereafter • Medications for participants in the intensive-treatment group were adjusted on a monthly basis to target a systolic blood pressure of less than 120 mm Hg.

	• Dose adjustment was based on a mean of three blood-pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest • The measurements were made with the use of an automated measurement system (Model 907, Omron Healthcare).
Comparator	• Participants were assigned to a systolic blood-pressure target of less than 140 mm Hg (the standard-treatment group). • For participants in the standard treatment group, medications were adjusted to target a systolic blood pressure of 135 to 139 mm Hg, and the dose was reduced if systolic blood pressure was less than 130 mm Hg on a single visit or less than 135 mm Hg on two consecutive visits.
Number of participants	1562
Duration of follow-up	Mean 3.1 years
Indirectness	None
Additional comments	• Number needed to treat (NNT) and number needed to harm (NNH) were calculated

Study arms

Intensive BP control (N = 779)

SBP < 120mmHg

Standard BP control (N = 783)

SBP <140mmHg

Characteristics

Arm-level characteristics

Characteristic	Intensive BP control (N = 779)	Standard BP control (N = 783)
Male (n (%)) Sample size	n = 577 ; % = 74	n = 604 ; % = 77
Age (years) Mean (SD)	70.6 (9.3)	70.1 (9.2)
> 75 years Mean (SD)	302 (38.8)	274 (35)
Non Hispanic Black Sample size	n = 145 ; % = 18.6	n = 157 ; % = 20.1
Hispanic Sample size	n = 67 ; % = 8.6	n = 66 ; % = 8.4
Non Hispanic white Sample size	n = 554 ; % = 71.1	n = 552 ; % = 70.5
Other Sample size	n = 13 ; % = 1.7	n = 8 ; % = 1
Black Sample size	n = 148 ; % = 19	n = 162 ; % = 20.7

Characteristic	Intensive BP control (N = 779)	Standard BP control (N = 783)
Systolic blood pressure Mean (SD)	138.8 (16.1)	137.6 (15.7)
Diastolic blood pressure Mean (SD)	75.6 (12.3)	73.9 (11.9)
Chronic kidney disease (n (%)) Sample size	n = 276 ; % = 35.4	n = 280 ; % = 35.8
Systolic blood pressure Nominal	121.6	134
Diastolic blood pressure Nominal	65.2	71.4
Number of antihypertensive agents per patient at baseline **Mean (SD)**	2.1 (1.0)	2.1 (1.0)

Outcomes

Study timepoints

- 3.1 year (Median follow up time period)

Results - Hazard ratios

Outcome	**Intensive BP control vs Standard BP control, 3.1 year, N2 = 779, N1 = 783**
Death from any cause Hazard ratio/95% CI	0.67 (0.45 to 1)
Stroke Hazard ratio/95% CI	1.69 (0.84 to 3.39)
Myocardial infarction Hazard ratio/95% CI	1.03 (0.64 to 1.64)
Heart failure Hazard ratio/95% CI	0.66 (0.38 to 1.15)
Injurious falls Hazard ratio/p value	1.02 (0.93)
Acute kidney injury Hazard ratio/p value	1.57 (0.049)

Results - raw data

Outcome	**Intensive BP control, 3.1 year, N = 779**	**Standard BP control, 3.1 year, N = 783**
All-cause mortality (Number of patients with an event)	n = 45 ; % = 5.8	n = 65 ; % = 8.3

Outcome	Intensive BP control, 3.1 year, N = 779	Standard BP control, 3.1 year, N = 783
No of events		
Stroke (Number of patients with an event) No of events	n = 22 ; % = 2.8	n = 13 ; % = 1.7
Myocardial infarction (Number of patients with an event) No of events	n = 38 ; % = 4.9	n = 36 ; % = 4.6
Heart failure (Number of patients with an event) No of events	n = 22 ; % = 2.8	n = 33 ; % = 4.2
Acute kidney injury or acute renal failure (Number of patients with an event) No of events	n = 51 ; % = 6.5	n = 35 ; % = 4.5
Injurious fall (Number of patients with an event) No of events	n = 26 ; % = 3.3	n = 27 ; % = 3.4

All-cause mortality - Polarity - Lower values are better

Stroke - Polarity - Lower values are better

Myocardial infarction - Polarity - Lower values are better

Heart failure - Polarity - Lower values are better

Acute kidney injury or acute renal failure - Polarity - Lower values are better

Injurious fall - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All cause mortality - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Stroke - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Myocardial infarction - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Heart failure - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Acute Kidney Injury/ Acute renal failure - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Injurious falls - 3.1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information regarding adherence)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(limited information on missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(indirect BP measurement method)*

Appendix E – Forest plots

Figure 2: Lower BP target versus standard BP target in adults with hypertension and CVD – all-cause mortality

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Mixed age: <80 years and ≥80 years						
PAST BP (Mant 2016)	2	266	1	263	0.3%	1.98 [0.18, 21.68]
PRESERVE (Markus 2021)	1	55	2	56	0.6%	0.51 [0.05, 5.45]
RESPECT (Kitagawa 2019)	30	633	37	630	10.8%	0.81 [0.50, 1.29]
SPRINT 2015 (from Saiz 2020)	45	779	65	783	18.8%	0.70 [0.48, 1.00]
SPS3 (Benavente 2013)	106	1501	101	1519	29.1%	1.06 [0.82, 1.38]
Subtotal (95% CI)		**3234**		**3251**	**59.5%**	**0.90 [0.74, 1.09]**
Total events	184		206			
Heterogeneity: Chi² = 4.26, df = 4 (P = 0.37); I² = 6%						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.1.2 All aged <80 years						
ACCORD BP 2010 (from Saiz 2020)	78	772	64	759	18.7%	1.20 [0.87, 1.64]
HOT 1998 (from Saiz 2020)	127	2168	56	1064	21.8%	1.11 [0.82, 1.51]
Subtotal (95% CI)		**2940**		**1823**	**40.5%**	**1.15 [0.93, 1.44]**
Total events	205		120			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.21)						
Total (95% CI)		**6174**		**5074**	**100.0%**	**1.00 [0.87, 1.16]**
Total events	389		326			
Heterogeneity: Chi² = 7.12, df = 6 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 2.77, df = 1 (P = 0.10), I² = 63.9%						

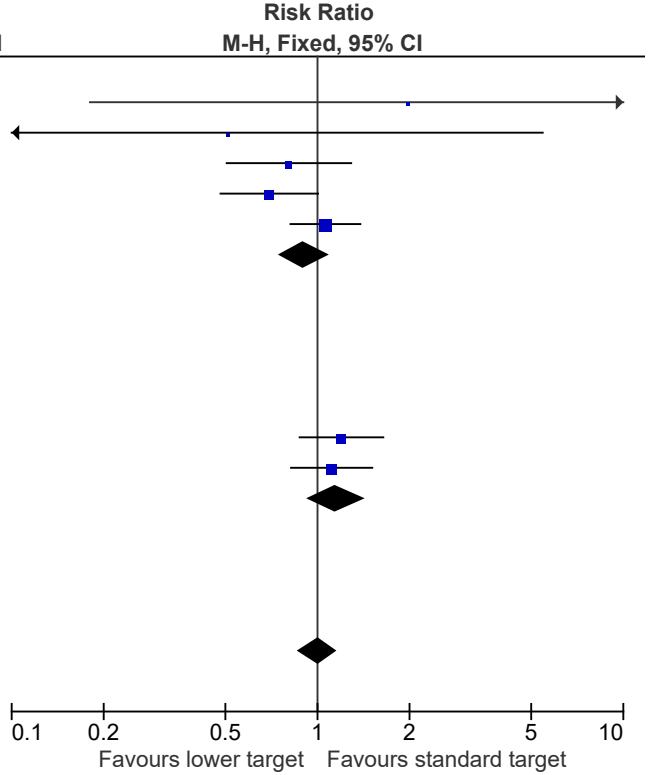


Figure 3: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – all-cause mortality (HR)

Study or Subgroup	log[Hazard Ratio]	SE	Lower BP target Total	Standard BP target Total	Weight	Hazard Ratio IV, Fixed, 95% CI
RESPECT (Kitagawa 2019)	-0.2231	0.2501	633	630	16.9%	0.80 [0.49, 1.31]
SPRINT (Vlachopoulos 2019)	-0.4005	0.2031	779	783	25.6%	0.67 [0.45, 1.00]
SPS3 (Benavente 2013)	0.0296	0.1354	1501	1519	57.6%	1.03 [0.79, 1.34]
Total (95% CI)			**2913**	**2932**	**100.0%**	**0.88 [0.72, 1.08]**

Heterogeneity: Chi² = 3.30, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 1.20 (P = 0.23)

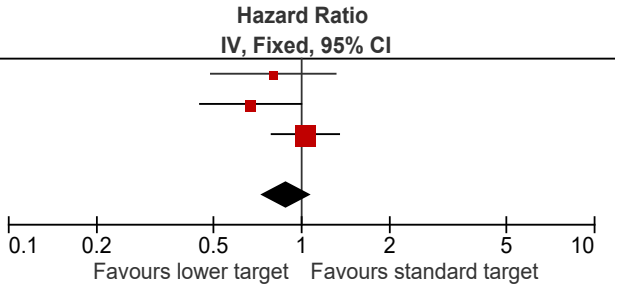


Figure 4: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – stroke

Study or Subgroup	Lower BP target Events	Lower BP target Total	Standard BP target Events	Standard BP target Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PAST BP (Mant 2016)	0	266	3	263	1.6%	0.14 [0.01, 2.72]
PRESERVE (Markus 2021)	3	55	3	56	1.3%	1.02 [0.21, 4.83]
RESPECT (Kitagawa 2019)	39	633	52	630	23.4%	0.75 [0.50, 1.11]
SPRINT (Vlachopoulos 2019)	22	779	13	783	5.8%	1.70 [0.86, 3.35]
SPS3 (Benavente 2013)	125	1501	152	1519	67.9%	0.83 [0.66, 1.04]
Total (95% CI)		**3234**		**3251**	**100.0%**	**0.85 [0.71, 1.03]**
Total events	189		223			

Heterogeneity: Chi² = 5.92, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 1.66 (P = 0.10)

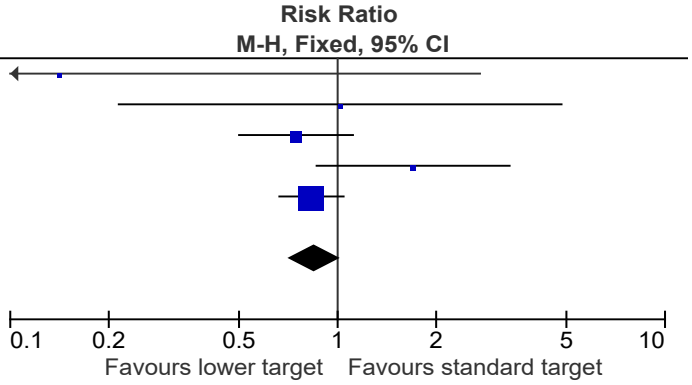


Figure 5: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – stroke (HR)

Study or Subgroup	log[Hazard Ratio]	SE	Lower BP target Total	Standard BP target Total	Weight	Hazard Ratio IV, Fixed, 95% CI
RESPECT (Kitagawa 2019)	-0.3147	0.2034	633	630	23.9%	0.73 [0.49, 1.09]
SPRINT (Vlachopoulos 2019)	0.5247	0.3567	779	783	7.8%	1.69 [0.84, 3.40]
SPS3 (Benavente 2013)	-0.2107	0.1202	1501	1519	68.4%	0.81 [0.64, 1.03]
Total (95% CI)			**2913**	**2932**	**100.0%**	**0.84 [0.69, 1.02]**

Heterogeneity: Chi² = 4.41, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.80 (P = 0.07)

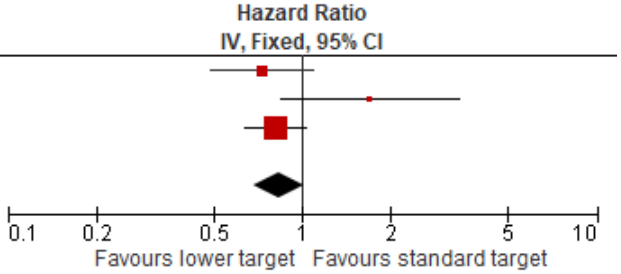


Figure 6: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – myocardial infarction

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PAST BP (Mant 2016)	1	266	1	263	1.2%	0.99 [0.06, 15.72]
RESPECT (Kitagawa 2019)	5	633	4	630	5.0%	1.24 [0.34, 4.61]
SPRINT (Vlachopoulos 2019)	38	779	36	783	44.5%	1.06 [0.68, 1.66]
SPS3 (Benavente 2013)	36	1501	40	1519	49.3%	0.91 [0.58, 1.42]
Total (95% CI)		**3179**		**3195**	**100.0%**	**1.00 [0.73, 1.35]**
Total events	80		81			

Heterogeneity: Chi² = 0.34, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)

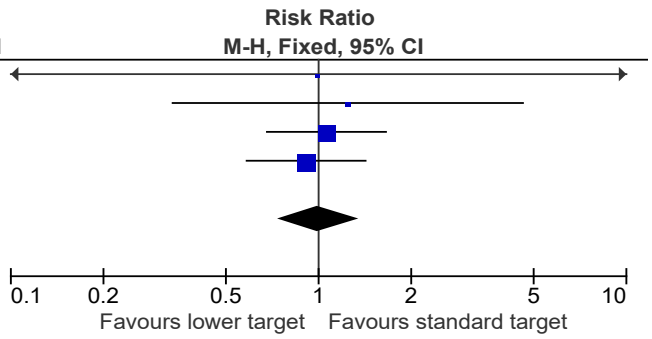


Figure 7: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – myocardial infarction (HR)

Study or Subgroup	log[Hazard Ratio]	SE	Lower BP target Total	Standard BP target Total	Weight	Hazard Ratio IV, Fixed, 95% CI
RESPECT (Kitagawa 2019)	0.207	0.6713	633	630	5.8%	1.23 [0.33, 4.58]
SPRINT (Vlachopoulos 2019)	0.0296	0.2428	779	783	44.7%	1.03 [0.64, 1.66]
SPS3 (Benavente 2013)	-0.1278	0.2306	1501	1519	49.5%	0.88 [0.56, 1.38]
Total (95% CI)			**2913**	**2932**	**100.0%**	**0.96 [0.70, 1.32]**

Heterogeneity: Chi² = 0.36, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

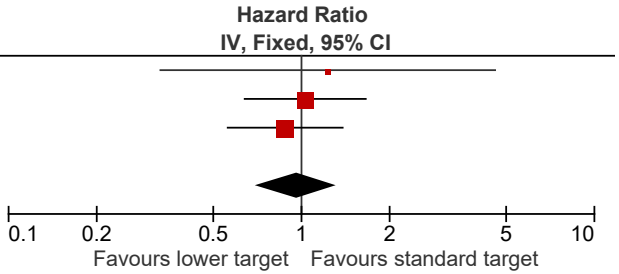


Figure 8: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – heart failure

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESPECT (Kitagawa 2019)	5	633	3	630	8.4%	1.66 [0.40, 6.91]
SPRINT (Vlachopoulos 2019)	22	779	33	783	91.6%	0.67 [0.39, 1.14]
Total (95% CI)		**1412**		**1413**	**100.0%**	**0.75 [0.46, 1.23]**
Total events	27		36			

Heterogeneity: Chi² = 1.36, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 1.13 (P = 0.26)

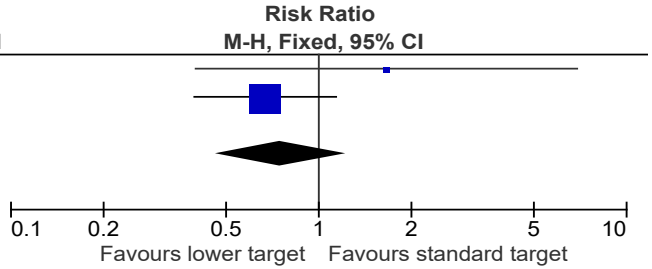


Figure 9: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – vascular procedures

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Risk Ratio M-H, Fixed, 95% CI
RESPECT (Kitagawa 2019)	10	633	11	630	0.90 [0.39, 2.12]

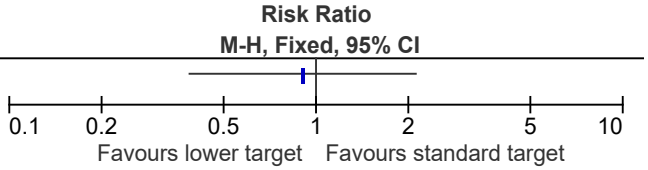


Figure 10: Lower BP target versus standard BP target in adults aged <80 years with hypertension and CVD – total cardiovascular events

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.15.2 All aged <80 years						
ACCORD BP 2010 (from Saiz 2020)	131	772	154	759	56.5%	0.84 [0.68, 1.03]
HOT 1998 (from Saiz 2020)	172	2168	89	1064	43.5%	0.95 [0.74, 1.21]
Subtotal (95% CI)		**2940**		**1823**	**100.0%**	**0.89 [0.75, 1.04]**
Total events	303		243			

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.44); I² = 0%

Test for overall effect: Z = 1.50 (P = 0.13)

Test for subgroup differences: Not applicable

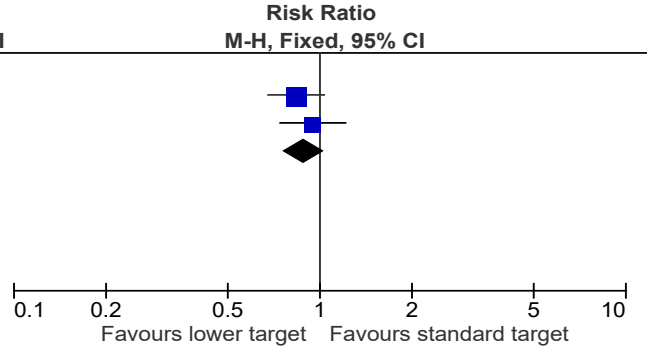


Figure 11: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – resource use (emergency admissions)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
PAST BP (Mant 2016)	0.4447	0.3158	1.56 [0.84, 2.90]

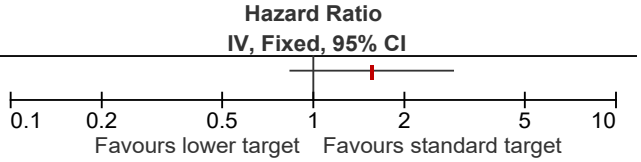
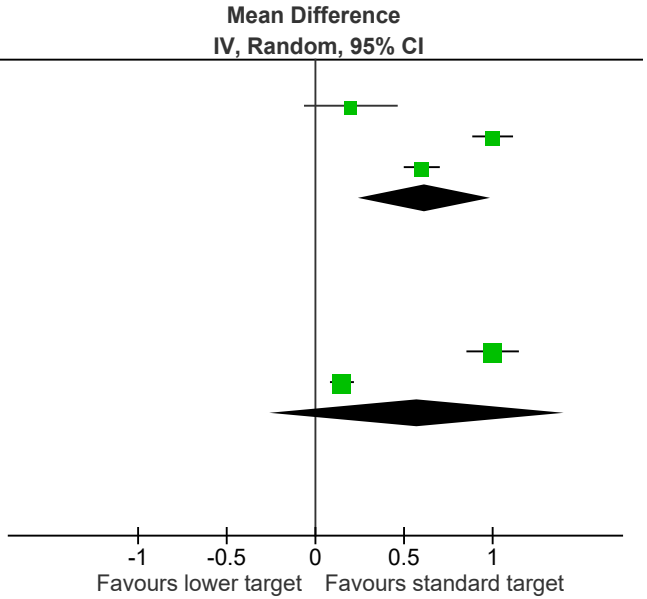


Figure 12: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD – resource use (number of antihypertensive drugs at end of trial)

Study or Subgroup	Lower BP target Mean	SD	Total	Standard BP target Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.10.1 Mixed age: <80 years and ≥80 years								
PAST BP (Mant 2016)	2.1	1.52	266	1.9	1.52	263	30.4%	0.20 [-0.06, 0.46]
SPRINT 2015 (from Saiz 2020)	3	1	712	2	1.1	698	34.7%	1.00 [0.89, 1.11]
SPS3 (Benavente 2013)	2.4	1.3	1501	1.8	1.4	1519	34.9%	0.60 [0.50, 0.70]
Subtotal (95% CI)			**2479**			**2480**	**100.0%**	**0.62 [0.25, 0.99]**
Heterogeneity: Tau² = 0.10; Chi² = 46.30, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 3.25 (P = 0.001)								
2.10.2 All age <80 years								
ACCORD BP 2010 (from Saiz 2020)	3.6	1.3	592	2.6	1.2	593	49.7%	1.00 [0.86, 1.14]
HOT 1998 (from Saiz 2020)	1.9	0.79	1809	1.75	0.77	895	50.3%	0.15 [0.09, 0.21]
Subtotal (95% CI)			**2401**			**1488**	**100.0%**	**0.57 [-0.26, 1.41]**
Heterogeneity: Tau² = 0.36; Chi² = 114.86, df = 1 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 1.35 (P = 0.18)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%								



Heterogeneity unexplained by subgroup analysis, therefore random effects applied

Figure 13: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD –withdrawal due to adverse events

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 Mixed age: <80 years and ≥80 years						
PAST BP 2016 (from Saiz 2020)	17	154	1	141	100.0%	15.56 [2.10, 115.45]
Subtotal (95% CI)		**154**		**141**	**100.0%**	**15.56 [2.10, 115.45]**
Total events	17		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.68 (P = 0.007)						
2.11.2 All aged <80 years						
HOT 1998 (from Saiz 2020)	5	266	1	129	100.0%	2.42 [0.29, 20.54]
Subtotal (95% CI)		**266**		**129**	**100.0%**	**2.42 [0.29, 20.54]**
Total events	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						

Test for subgroup differences: Chi² = 1.55, df = 1 (P = 0.21), I² = 35.4%

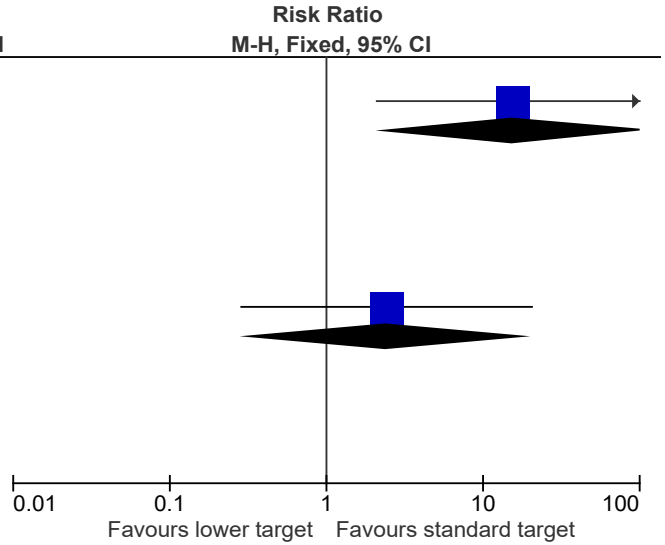


Figure 14: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD –Acute kidney injury

Study or Subgroup	Favours lower target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PRESERVE (Markus 2021)	1	55	0	56	1.4%	3.05 [0.13, 73.38]
SPRINT (Vlachopoulos 2019)	51	779	35	783	98.6%	1.46 [0.96, 2.23]
Total (95% CI)		**834**		**839**	**100.0%**	**1.49 [0.98, 2.25]**
Total events	52		35			
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						

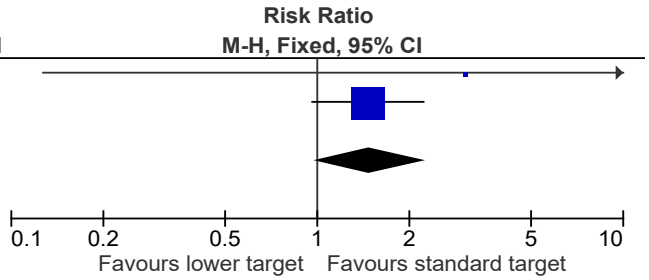


Figure 15: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD –worsening renal function

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Risk Ratio M-H, Fixed, 95% CI
RESPECT (Kitagawa 2019)	6	663	1	630	5.70 [0.69, 47.22]

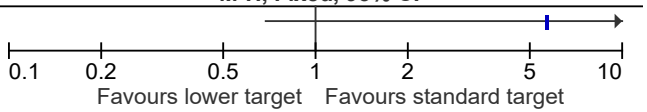
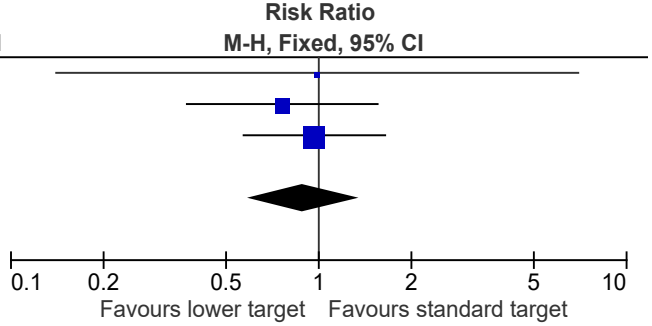


Figure 16: Lower BP target versus standard BP target in adults (aged <80 or ≥80 years) with hypertension and CVD –injurious falls

Study or Subgroup	Lower BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PAST BP (Mant 2016)	2	266	2	263	4.4%	0.99 [0.14, 6.97]
RESPECT (Kitagawa 2019)	13	633	17	630	37.1%	0.76 [0.37, 1.55]
SPRINT (Vlachopoulos 2019)	26	779	27	783	58.6%	0.97 [0.57, 1.64]
Total (95% CI)		**1678**		**1676**	**100.0%**	**0.89 [0.59, 1.35]**
Total events	41		46			

Heterogeneity: Chi² = 0.29, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



Appendix F – GRADE tables

Table 11: Clinical evidence profile: Clinical evidence summary: lower BP target versus standard BP target in adults aged <80 years

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
All-cause mortality (follow up: range 3.8 years to 4.7 years)											
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	205/2940 (7.0%)	120/1823 (6.6%)	RR 1.15 (0.93 to 1.44)	10 more per 1,000 (from 5 fewer to 29 more)	⊕◯◯◯ VERY LOW
Total cardiovascular events (follow up: range 3.8 years to 4.7 years)											
2	randomised trials	not serious	not serious	serious [d]	serious [e]	none	303/2940 (10.3%)	243/1823 (13.3%)	RR 0.89 (0.75 to 1.04)	15 fewer per 1,000 (from 33 fewer to 5 more)	⊕⊕◯◯ LOW
Resource use: Number of antihypertensive drugs needed per participant at the end of study (follow up: range 3.8 years to 4.7 years)											
2	randomised trials	serious [f]	very serious [g]	serious [b]	serious [h]	none	2401	1488	-	MD 0.57 higher (0.26 lower to 1.41 higher)	⊕◯◯◯ VERY LOW
Participant withdrawals due to adverse effects (follow up: mean 3.8 years)											
1	randomised trials	serious [f]	not serious	serious [i]	very serious [j]	none	5/266 (1.9%)	1/129 (0.8%)	RR 2.42 (0.29 to 20.54)	11 more per 1,000 (from 6 fewer to 151 more)	⊕◯◯◯ VERY LOW

a. Majority of the evidence based on post-hoc subgroup analysis of RCT data
b. Majority of the evidence indirect due to BP target threshold definitions and population definition excluded TIA
c. 95% CI crosses the line of no effect
d. Indirect outcome measure: composite including CV event and mortality
e. 95% CI crosses one MID
f. Patients and caregivers not blinded to allocation
g. I^2 = 99%
h. 95%CI crosses one MID (MID= ±0.49)
i. Indirect BP target threshold and population definition excluded TIA
j. 95% CI crosses both MIDs

Table 12: Clinical evidence profile: Clinical evidence summary: lower BP target versus standard BP target in a mixed population including adults aged <80 and ≥80 years

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
All-cause mortality (follow up: range 1 years to 3.9 years)											
5	randomised trials	not serious	not serious	serious [a]	serious [b]	none	184/3234 (5.7%)	206/3251 (6.3%)	RR 0.90 (0.74 to 1.09)	6 fewer per 1,000 (from 16 fewer to 6 more)	⊕⊕◯◯ LOW
*All-cause mortality (HR) (follow up: range 3.3 years to 3.9 years)**											
3	*randomised trials*	*not serious*	*not serious*	*serious [c]*	*serious [d]*	*none*	*181/2913 (6.2%)*	*203/2932 (6.9%)*	*HR 0.88 (0.72 to 1.08)*	*8 fewer per 1,000 (from 19 fewer to 5 more)*	*⊕⊕◯◯ LOW*
Stroke (follow up: range 1 years to 3.9 years)											
5	randomised trials	not serious	not serious	serious [c]	serious [d]	none	189/3234 (5.8%)	223/3251 (6.9%)	RR 0.85 (0.71 to 1.03)	10 fewer per 1,000 (from 20 fewer to 0 fewer)[e]	⊕⊕◯◯ LOW
*Stroke (HR) (follow up: range 3.3 years to 3.9 years)**											

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
3	*randomised trials*	*not serious*	*not serious*	*serious [c]*	*serious [d]*	*none*	*186/2913 (6.4%)*	*217/2932 (7.4%)*	*HR 0.84 (0.69 to 1.02)*	*11 fewer per 1,000 (from 22 fewer to 1 more)*	*⨁⨁◯◯ LOW*
Myocardial infarction (follow up: range 1 years to 3.9 years)											
4	randomised trials	serious [f]	not serious	serious [a]	very serious [g]	none	80/3179 (2.5%)	81/3195 (2.5%)	RR 1.00 (0.73 to 1.35)	0 fewer per 1,000 (from 7 fewer to 9 more)	⨁◯◯◯ VERY LOW
*Myocardial infarction (HR) (follow up: range 3.3 years to 3.9 years)**											
3	*randomised trials*	*serious [f]*	*not serious*	*serious [a]*	*very serious [g]*	*none*	*79/2913 (2.7%)*	*80/2932 (2.7%)*	*HR 0.96 (0.70 to 1.32)*	*1 fewer per 1,000 (from 8 fewer to 9 more)*	*⨁◯◯◯ VERY LOW*
Heart failure (follow up: range 3.3 years to 3.9 years)											
2	randomised trials	serious [f]	not serious	very serious [h]	very serious [g]	none	27/1412 (1.9%)	36/1413 (2.5%)	RR 0.75 (0.46 to 1.23)	6 fewer per 1,000 (from 14 fewer to 6 more)	⨁◯◯◯ VERY LOW

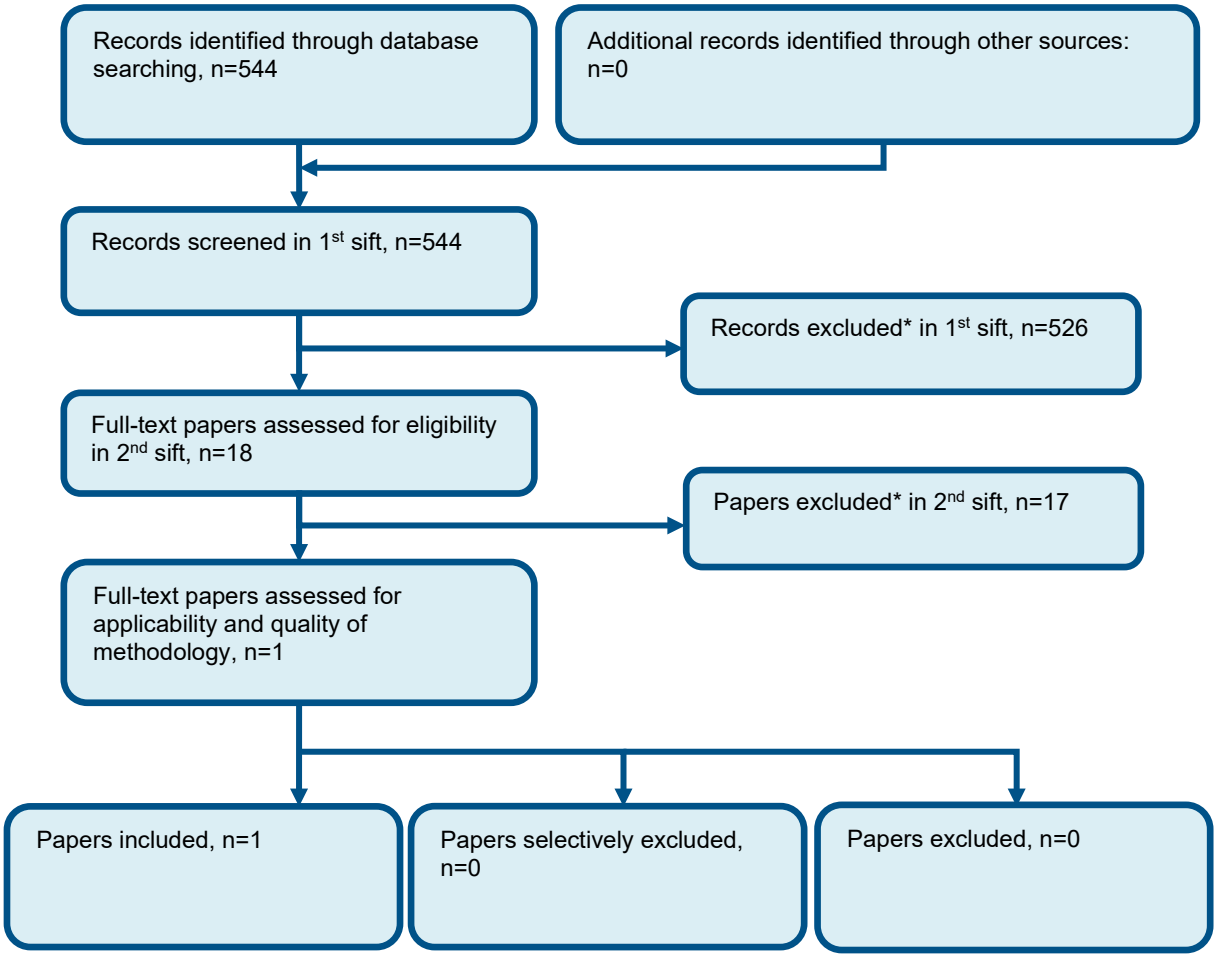
Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Vascular procedures (coronary intervention or surgery) (follow up: mean 3.9 years)											
1	randomised trials	not serious	not serious	not serious	very serious [g]	none	10/633 (1.6%)	11/630 (1.7%)	RR 0.90 (0.39 to 2.12)	2 fewer per 1,000 (from 11 fewer to 20 more)	⊕⊕◯◯ LOW
Resource use: Number of antihypertensive drugs needed per participant at the end of study (follow up: range 1 years to 3.7 years)											
3	randomised trials	serious [i]	very serious [j]	serious [a]	serious [k]	none	2479	2480	-	MD 0.62 higher (0.25 higher to 0.99 higher)	⊕◯◯◯ VERY LOW
Resource use: Mean number of drugs at end of follow up (follow up: mean 3.9 years)											
1	randomised trials	serious [i]	not serious	not serious	not serious [l]	none	633	630	-	MD 1.2 drugs higher	⊕⊕⊕◯ MODERATE
Resource use: Median number of GP visits (follow up: mean 1 years)											
1	randomised trials	serious [i]	not serious	very serious [m]	not serious [l]	none	266	263	-	median 1 visit higher	⊕◯◯◯ VERY LOW
Resource use: Median number of practice nurse visits (follow up: mean 1 years)											
1	randomised trials	serious [i]	not serious	very serious [m]	not serious [l]	none	266	263	-	median 1 visit higher	⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Resource use (emergency admission) (follow up: mean 1 years)											
1	randomised trials	serious [n]	not serious	serious [m]	serious [d]	none	266 (12.8% per year)	263 (7.8% per year)	HR 1.56 (0.84 to 2.90)	Not available	⨁◯◯◯ VERY LOW
Participant withdrawals due to adverse effects (follow up: mean 1 years)											
1	randomised trials	very serious [o]	not serious	very serious [m]	not serious	none	17/154 (11.0%)	1/141 (0.7%)	RR 15.56 (2.10 to 115.45)	103 more per 1,000 (from 8 more to 812 more)	⨁◯◯◯ VERY LOW
AKI (follow up: range 2.0 years to 3.3 years)											
2	randomised trials	serious [f]	not serious	serious [p]	serious [d]	none	52/834 (6.2%)	35/839 (4.2%)	RR 1.49 (0.98 to 2.25)	20 more per 1,000 (from 0 fewer to 40 more) [e]	⨁◯◯◯ VERY LOW
Worsening renal function (follow up: mean 3.9 years)											
1	randomised trials	serious [n]	not serious	serious [q]	very serious [g]	none	6/663 (0.9%)	1/630 (0.2%)	RR 5.70 (0.69 to 47.22)	7 more per 1,000 (from 0 fewer to 73 more)	⨁◯◯◯ VERY LOW
Injurious falls (follow up: range 1 years to 3.9 years)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lower BP targets**	**Standard BP targets**	**Relative (95% CI)**	**Absolute (95% CI)**	
3	randomised trials	serious [f]	not serious	very serious [r]	very serious [g]	none	41/1678 (2.4%)	46/1676 (2.7%)	RR 0.89 (0.59 to 1.35)	3 fewer per 1,000 (from 11 fewer to 10 more)	⊕◯◯◯ VERY LOW

** For these outcomes both the dichotomous and time-to-event data are reported, but the primary measure for decision-making was the dichotomous data because there was very little difference in the effect estimates from the hazard ratios and risk ratios, while the risk ratio analysis has the benefit of including all available data.*
a. Majority of the evidence indirect due to BP target threshold definitions and/or method of blood pressure measurement
b. 95% CI crosses the line of no effect
c. Majority of the evidence indirect due to BP target threshold definitions
d. 95% CI crosses one MID
e. Calculated from risk difference because zero events in one arm of one trial
f. Majority of the evidence at high risk of attrition bias
g. 95% CI crosses both MIDs
h. Majority of the evidence indirect due to BP target threshold definitions and method of blood pressure measurement
i. Patients and caregivers not blinded to allocation
j. I^2 = 96%
k. 95% crosses one MID (MID= ±0.7)
l. Imprecision could not be assessed
m. Indirect BP target threshold and hypertension definition
n. High risk of attrition bias
o. Patients and caregivers not blinded to allocation and high risk of attrition bias
p. Majority of the evidence indirect due to method of blood pressure measurement
q. Indirect BP target threshold
r. Majority of the evidence indirect due to BP target threshold definitions and/or method of blood pressure measurement and/or outcome definition

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Pendaloza-Ramos 2016[22]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model utilising patient-level data from the PAST-BP RCT. **Approach to analysis:** Markov model with health states: previous stroke/TIA (no new event), new stroke, post-new stroke, MI, post MI, unstable angina, post unstable angina and death. One-year cycles. The reductions in SBP in the PAST-BP trial were converted to reductions in the probabilities of CVD events using a published meta-analysis. **Perspective:** UK NHS & PSS **Time horizon:** lifetime	**Population:** People with a history of stroke or TIA, and SBP ≥125mmHg recruited from primary care. **Cohort settings:** Start age: 70 years Male: 59% **Intervention 1:** Standard target (<140mmHg systolic blood pressure). Active management. **Intervention 2:** Lower target (<130mmHg systolic blood pressure or 10mmHg reduction from baseline if this was <140 mmHg). Active management.	**Total costs (mean per patient):** Intervention 1: £9,889 Intervention 2: £9720 Incremental (2−1): -£169 (95% CI: NR; p=NR) **Currency & cost year:** 2011/12 UK pounds **Cost components incorporated:** Antihypertensive drugs, GP and nurse consultations and acute and long terms costs of cardiovascular events.	**QALYs (mean per patient):** Intervention 1: 7.47 Intervention 2: 7.55 Incremental (2−1): 0.08 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 was dominant (lower costs and higher QALYs) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 90%/~95% **Analysis of uncertainty:** Sensitivity analyses explored varying the time horizon, changing costs of disease and the initial cost for the intensive BP lowering group by 30%, varying the effect size of the intensive BP lowering arm according to the 95% CI of the BP reduction difference achieved at 12 months, incorporating a utility decrement dur to antihypertensive medication by reducing utility values (multiplicatively) for the initial health state in the intensive BP lowering group by up to 10%. The lower target was no longer cost effective if the lower bound of the 95% CI for BP reduction was used, if a time horizon of only 1 year was used and if intensive BP lowering is associated with a 2% or more reduction in quality of life (it remains less costly because of the

Treatment effect duration:[(a)] lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%				reduction in cardiovascular events but also results in less QALYs).
Data sources				
Health outcomes: Annual transition probabilities determining the risk of a cardiovascular event were based on the results of the PROGRESS trial. Age-related risk reductions for CHD and stroke associated with subsequent reductions in SBP observed at 12 months in the PAST-BP trial were obtained from a meta analysis by Law et al 2009.[18] The risk reduction for CHD was applied to both MI and UA. Treatment effect was assumed to persist beyond one year. **Quality-of-life weights:** Utility for the initial health state of previous stroke/TIA (with no new event) was based on the PAST-BP RCT mean baseline EQ-5D-3L score; the tariff used is not stated but assumed to be UK as PAST-BP and this CUA are in the UK setting. Utilities for acute and post-acute new CVD event states estimated by multiplying this starting utility with that of the new CVD event. CVD event utilities were based on values used in the NICE Lipid Modification Guideline analysis 2008; instrument not stated. Reducing utility with age was incorporated into the model. **Cost sources:** Annual cost of antihypertensive drugs and consultations with the standard and lower target was based on analysis of the PAST-BP RCT with UK unit costs applied. Acute and longer term costs associated with CVD events were based on the published literature inflated to 2011/12 costs.				
Comments				
Source of funding: NIHR. **Limitations:** Population doesn't exactly match protocol – not all hypertensive. Intervention doesn't exactly match protocol. UK resource use from 2009-12 (PAST-BP) and older (published sources) and 2011/12 costs may not current UK context. Based on one of several studies included in clinical review and so does not reflect all available clinical evidence. Model uses blood pressure reduction from clinical trial to model differences in clinical events rather than direct evidence of effect on clinical events as specified in clinical review protocol for outcomes. Unclear if baseline event probabilities are from best available source; based on PROGRESS RCT which recruited from Asia, Australia and Europe 1995 to 2001 and so may not reflect current real-world event rates for England; rationale for selection not described. PAST-BP reported an increase in emergency admissions with the lower target but this does not appear to be included in the cost analysis. Uncertainty around baseline event probabilities, blood pressure reduction and the relationship between blood pressure reduction and reduction in clinical events do not appear to be incorporated into the probabilistic analysis and so uncertainty will be underestimated. **Other:**				
Overall applicability:[(c)] Partially applicable		**Overall quality:**[(d)] Potentially serious limitations		

Abbreviations: 95% CI = 95% confidence interval; BP = blood pressure; CUA = cost–utility analysis; CHD = coronary heart disease; CVD = cardiovascular disease; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years; RCT = randomised clinical trial; TIA = transient ischemic attack; UA = unstable angina.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

Economic modelling was not undertaken.

Appendix J – Excluded studies

Clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
(2019) Optimal blood pressure control in patients with acute ischaemic stroke: ENCHANTED trial. Internist	- Unavailable
Agarwal, A., Cheung, A. K., Ma, J. et al. (2019) Effect of Baseline Kidney Function on the Risk of Recurrent Stroke and on Effects of Intensive Blood Pressure Control in Patients With Previous Lacunar Stroke: A Post Hoc Analysis of the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes). Journal of the American Heart Association 8(16): e013098	- Secondary publication of an included study that does not provide any additional relevant information
Aggarwal, R., Petrie, B., Bala, W. et al. (2019) Mortality Outcomes With Intensive Blood Pressure Targets in Chronic Kidney Disease Patients. Hypertension 73(6): 1275-1282	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Review article but not a systematic review
Aggarwal, R., Steinkamp, J., Chiu, N. et al. (2018) Intensive Blood Pressure Targets for Diabetic and Other High-Risk Populations: A Pooled Individual Patient Data Analysis. Hypertension 71(5): 833-839	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Alborzi, A., Attar, A., Sayadi, M. et al. (2021) The Effects of Intensive Blood Pressure Control on Cardiovascular Outcomes Based on 10-Year ASCVD Risk Score: An Analysis of a Clinical Trial. Cardiology Research & Practice 2021: 6635345	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Almalki, Z. S., Iqbal, M. S., Alablan, F. M. et al. (2020) Long Term Cost-Effectiveness of a Systolic Blood Pressure Goal of <120 mmHg in Hypertensive Patients Without Diabetes Mellitus. Value in Health Regional Issues 21: 157-163	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study design: health economic analysis
Anderson, C. S., Sharma, V., Huang, Y. et al. (2012) The ENhanced Control of Hypertension ANd Thrombolysis strokE StuDy (ENCHANTED): evaluation of low-dose rtPA and early intensive blood pressure (BP) lowering in acute ischaemic stroke. 21st european stroke conference 2012	- Conference abstract
Anderson, C., Lavados, P., Sharma, V. et al. (2015) Intensive blood pressure lowering in acute ischemic stroke: ENCHANTED trial. International stroke conference 2015	- Conference abstract
Anderson, C., Sharma, V., Huang, Y. et al. (2013) ENCHANTED trial of low-dose tpa and early intensive blood pressure lowering in acute ischaemic stroke. International stroke conference 2013	- Conference abstract

Study	Exclusion reason
Anonymous (2017) Hypertension Targeting 120 mmHg: survival benefit after 3 years, but high renal risk. Prescrire International 26(178): 21-22	- Secondary publication of an included study that does not provide any additional relevant information
Arguedas, Ja; Leiva, V; Wright, Jm (2020) Blood pressure targets in adults with hypertension. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Systematic review used as source of primary studies
Arguedas, Ja; Leiva, V; Wright, Jm (2013) Blood pressure targets for hypertension in people with diabetes mellitus. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Aschmann, H. E., Boyd, C. M., Robbins, C. W. et al. (2019) Balance of benefits and harms of different blood pressure targets in people with multiple chronic conditions: a quantitative benefit-harm assessment. BMJ Open 9(8): e028438	- Systematic review used as source of primary studies - Study design: health economic analysis
Aydin, V., Akici, A., Sakarya, S. et al. (2020) Baseline characteristics predicting clinical outcomes and serious adverse events in middle-aged hypertensive women: a subanalysis of the SPRINT in women aged <65 years. Turkish Journal of Medical Sciences 50(5): 1298-1306	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Berlowitz, D. R., Foy, C., Conroy, M. et al. (2020) Impact of Intensive Blood Pressure Therapy on Concern about Falling: Longitudinal Results from the Systolic Blood Pressure Intervention Trial (SPRINT). Journal of the American Geriatrics Society 68(3): 614-618	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Blackburn, D. J., Krishnan, K., Fox, L. et al. (2013) Prevention of Decline in Cognition after Stroke Trial (PODCAST): a study protocol for a factorial randomised controlled trial of intensive versus guideline lowering of blood pressure and lipids. Trials [Electronic Resource] 14: 401	- Study does not contain an outcome relevant to this review: Trial protocol only
Blood Pressure Lowering Treatment Trialists, Collaboration (2021) Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet 397(10285): 1625-1636	- Systematic review used as source of primary studies - Study does not contain comparison relevant to this review protocol
Blum, M. R., Scherzer, R., Ikeme, J. C. et al. (2020) Functional health and white matter hyperintensities as effect modifiers of blood pressure-lowering on cognitive function and vascular events in older Secondary Prevention of Small Subcortical Strokes trial participants. Journal of Hypertension 38(8): 1578-1585	- Secondary publication of an included study that does not provide any additional relevant information
Bohm, M., Schumacher, H., Teo, K. K. et al. (2019) Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. European Heart Journal 40(25): 2032-2043	- Study does not contain comparison relevant to this review protocol

Study	Exclusion reason
Bohm, M., Schumacher, H., Teo, K. K. et al. (2017) Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet 389(10085): 2226-2237	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Bohm, M., Schumacher, H., Teo, K. K. et al. (2018) Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120-140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. European Heart Journal 39(33): 3105-3114	- Study does not contain comparison relevant to this review protocol
Botchway, A., Buhnerkempe, M. G., Prakash, V. et al. (2020) Serious Adverse Events Cluster in Participants Experiencing the Primary Composite Cardiovascular Endpoint: A Post Hoc Analysis of the SPRINT Trial. American Journal of Hypertension 33(6): 528-533	- Study does not contain comparison relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Bress, A. P., King, J. B., Kreider, K. E. et al. (2017) Effect of Intensive Versus Standard Blood Pressure Treatment According to Baseline Prediabetes Status: A Post Hoc Analysis of a Randomized Trial. Diabetes Care 09: 09	- Secondary publication of an included study that does not provide any additional relevant information
Brunstrom, M. and Carlberg, B. (2018) Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Internal Medicine 178(1): 28-36	- Review article but not a systematic review - Study does not contain comparison relevant to this review protocol
Bundy, J. D., Li, C., Stuchlik, P. et al. (2017) Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiology 2(7): 775-781	- Systematic review used as source of primary studies - Study does not contain comparison relevant to this review protocol
Byrne, C., Pareek, M., Vaduganathan, M. et al. (2020) Intensive blood pressure lowering in different age categories: insights from the Systolic Blood Pressure Intervention Trial. European Heart Journal Cardiovascular Pharmacotherapy 6(6): 356-363	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Chen, C., Wang, X., Chen, X. et al. (2021) Disparities between Asian and Non-Asian Thrombolyzed Acute Ischemic Stroke Patients in the Enhanced Control of Hypertension and Thrombolysis Stroke Trial. Cerebrovascular Diseases: 1-7	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Chen, L. Y., Bigger, J. T., Hickey, K. T. et al. (2016) Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation and P-Wave Indices in the ACCORD Blood Pressure Trial. American Journal of Hypertension 29(11): 1276-1282	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
Cherniaeva, M. S. and Ostroumova, O. D. (2020) Target levels of blood pressure in patients with arterial hypertension and coronary heart disease. Arter. Hypertens. 26(1): 15-26	- Study not reported in English
Chi, G., Jamil, A., Jamil, U. et al. (2019) Effect of intensive versus standard blood pressure control on major adverse cardiac events and serious adverse events: A bivariate analysis of randomized controlled trials. Clinical and Experimental Hypertension 41(2): 160-167	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol - Population not relevant to this review protocol: >20% with CKD requiring lower BP target
Collard, D., Brouwer, T. F., Olde Engberink, R. H. G. et al. (2020) Initial Estimated Glomerular Filtration Rate Decline and Long-Term Renal Function During Intensive Antihypertensive Therapy: A Post Hoc Analysis of the SPRINT and ACCORD-BP Randomized Controlled Trials. Hypertension 75(5): 1205-1212	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Contreras, G., Lu, L., Tamariz, L. et al. (2020) Outcomes in adults with systolic blood pressure between 130 and 139 mmHg in Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial and Systolic Blood Pressure Intervention Trial. Journal of Hypertension 38(8): 1567-1577	- Systematic review used as source of primary studies
D'Anci, K. E., Tipton, K., Hedden-Gross, A. et al. (2020) Effect of Intensive Blood Pressure Lowering on Cardiovascular Outcomes: A Systematic Review Prepared for the 2020 U.S. Department of Veterans Affairs/U.S. Department of Defense Guidelines. Annals of Internal Medicine 173(11): 895-903	- Systematic review used as source of primary studies
Der Mesropian, P. J., Shaikh, G., Beers, K. H. et al. (2021) Effect of intensive blood pressure on the progression of non-diabetic chronic kidney disease at varying degrees of proteinuria. Journal of Investigative Medicine 69(5): 1035-1043	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Population not relevant to this review protocol: >20% with CKD requiring lower BP target
Dieter, B. P., Daratha, K. B., McPherson, S. M. et al. (2019) Association of Acute Kidney Injury with Cardiovascular Events and Death in Systolic Blood Pressure Intervention Trial. American Journal of Nephrology 49(5): 359-367	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Einecke, D. (2001) PROGRESS study examines transient cerebral ischemia and stroke patients. Future goals: attaining blood pressure control. MMW fortschritte der medizin 143(2627): 4-5	- Study not reported in English
Erviti, J., Saiz, L. C., Salzwedel, D. M. et al. (2019) Blood pressure targets for hypertension in people with chronic renal disease. Cochrane Database of Systematic Reviews 2019 (7)	- Population not relevant to this review protocol: >20% with CKD requiring lower BP target
Fatani, N., Dixon, D. L., Van Tassell, B. W. et al. (2021) Systolic Blood Pressure Time in Target Range and Cardiovascular Outcomes in	- Population not relevant to this review protocol: no subgroup data for those with established CVD

Study	Exclusion reason
Patients With Hypertension. Journal of the American College of Cardiology 77(10): 1290-1299	
Fei, Y.; Tsoi, M. F.; Cheung, B. M. Y. (2018) Determining the Optimal Systolic Blood Pressure for Hypertensive Patients: A Network Meta-analysis. Canadian Journal of Cardiology 34(12): 1581-1589	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Fletcher, K., Mant, J., McManus, R. et al. (2010) Protocol for Past BP: a randomised controlled trial of different blood pressure targets for people with a history of stroke of transient ischaemic attack (TIA) in primary care. BMC Cardiovascular Disorders 10: 37	Duplicate reference
Fletcher, K., Mant, J., McManus, R. et al. (2016) No title provided. NIHR Journals Library. Programme Grants for Applied Research 03: 03	- Secondary publication of an included study that does not provide any additional relevant information
Foy, A. J.; Nudy, M.; Naccarelli, G. (2021) a patient-level meta-analysis of intensive versus standard blood pressure control according to baseline diastolic blood pressure: the j-curve revisited. J. Am. Coll. Cardiol. 77(18): 1555-None	- Conference abstract
Foy, C. G., Lovato, L. C., Vitolins, M. Z. et al. (2018) Gender, blood pressure, and cardiovascular and renal outcomes in adults with hypertension from the Systolic Blood Pressure Intervention Trial. Journal of Hypertension 36(4): 904-915	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Frary, J. M. C., Pareek, M., Byrne, C. et al. (2021) Intensive blood pressure control appears to be effective and safe in patients with peripheral artery disease: the Systolic Blood Pressure Intervention Trial. European Heart Journal Cardiovascular Pharmacotherapy 7(3): e38-e40	- Secondary publication of an included study that does not provide any additional relevant information
Fukuda-Doi, M., Yamamoto, H., Koga, M. et al. (2020) Sex Differences in Blood Pressure-Lowering Therapy and Outcomes Following Intracerebral Hemorrhage: Results From ATACH-2. Stroke 51(8): 2282-2286	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Fukui, S., Higashio, K., Murao, S. et al. (2021) Optimal target blood pressure in critically ill adult patients with vasodilatory shock: a protocol for a systematic review and meta-analysis. BMJ open 11(3): e048512	- Study does not contain an intervention relevant to this review protocol: mean blood pressure target
Garrison, S. R., Kolber, M. R., Korownyk, C. S. et al. (2017) Blood pressure targets for hypertension in older adults. Cochrane Database of Systematic Reviews 2017 (8)	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Gitsels, L. A., Kulinskaya, E., Bakbergenuly, I. et al. (2019) Optimal SBP targets in routine clinical care. Journal of Hypertension 37(4): 837-843	- Population not relevant to this review protocol: no subgroup data for those with established CVD

Study	Exclusion reason
	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Gong, S., Lin, C., Zhang, D. et al. (2017) Effects of Intensive Blood Pressure Reduction on Acute Intracerebral Hemorrhage: A Systematic Review and Meta-analysis. Scientific Reports 7(1): 10694	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Group, S. P. S. Study, Benavente, O. R., Coffey, C. S. et al. (2013) Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 382(9891): 507-15	- Duplicate reference
Group, Sprint Mind Investigators for the SPRINT Research, Nasrallah, I. M., Pajewski, N. M. et al. (2019) Association of Intensive vs Standard Blood Pressure Control With Cerebral White Matter Lesions. JAMA 322(6): 524-534	- Study does not contain an outcome relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Group, Sprint Mind Investigators for the SPRINT Research, Williamson, J. D., Pajewski, N. M. et al. (2019) Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA 321(6): 553-561	- Study does not contain an outcome relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Group, Sprint Research, Lewis, C. E., Fine, L. J. et al. (2021) Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine 384(20): 1921-1930	- Secondary publication of an included study that does not provide any additional relevant information
Hansson, L. and Zanchetti, A. (1994) The Hypertension Optimal Treatment (HOT) Study--patient characteristics: randomization, risk profiles, and early blood pressure results. Blood Press 3(5): 322-7	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Hansson, L. and Zanchetti, A. (1997) The Hypertension Optimal Treatment (HOT) Study: 24-month data on blood pressure and tolerability. Blood Press 6(5): 313-7	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Ho, V., Stijacic-Cenzer, I., Lee, S. et al. (2020) Time to benefit for stroke reduction after more intensive blood pressure control in older adults. J. Am. Geriatr. Soc. 68(suppl1): S2-S3	- Conference abstract
Hong, K. S. (2017) Blood Pressure Management for Stroke Prevention and in Acute Stroke. Journal of Stroke 19(2): 152-165	- Review article but not a systematic review
Hornnes, A. H. and Poulsen, M. B. (2020) Blood pressure after follow-up in a stroke prevention clinic. Brain and Behavior 10(8): e01667	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Ilkun, O. L., Greene, T., Cheung, A. K. et al. (2020) The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood	- Population not relevant to this review protocol: no subgroup data for those with established CVD

Study	Exclusion reason
Pressure Lowering on Cardiovascular Outcomes and All-Cause Mortality in Type 2 Diabetes. Diabetes Care 43(8): 1878-1884	
Juraschek, S. P., Hu, J. R., Cluett, J. et al. (2020) Effects of intensive blood pressure treatment on orthostatic hypotension: an individual-level meta-analysis. Hypertension 76(suppl1)	- Conference abstract
Kamishima, K., Ogawa, H., Jujo, K. et al. (2019) Relationships between blood pressure lowering therapy and cardiovascular events in hypertensive patients with coronary artery disease and type 2 diabetes mellitus: The HIJ-CREATE sub-study. Diabetes Research & Clinical Practice 149: 69-77	- Study does not contain comparison relevant to this review protocol
Kan, S., Sun, R., Chai, S. et al. (2020) A clinical study on the association of clinical outcome and acute systolic blood pressure in cerebral hemorrhage patients. International Journal of Clinical Pharmacology & Therapeutics 58(3): 146-154	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Karmali, K. N., Lloyd-Jones, D. M., van der Leeuw, J. et al. (2018) Blood pressure-lowering treatment strategies based on cardiovascular risk versus blood pressure: A meta-analysis of individual participant data. PLoS Medicine / Public Library of Science 15(3): e1002538	- Study does not contain comparison relevant to this review protocol - Systematic review used as source of primary studies
Kaul, Sanjay (2020) Evidence for the universal blood pressure goal of< 130/80 mm Hg is strong: controversies in hypertension-con side of the argument. Hypertension 76(5): 1391-1399	- Review article but not a systematic review
Kikuchi, N., Ogawa, H., Kawada-Watanabe, E. et al. (2020) Impact of age on clinical outcomes of antihypertensive therapy in patients with hypertension and coronary artery disease: A sub-analysis of the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease. Journal of Clinical Hypertension 22(6): 1070-1079	- Study does not contain comparison relevant to this review protocol
Klarskov, P., Bang, L. E., Schultz-Larsen, P. et al. (2018) Intensive versus conventional blood pressure monitoring in a general practice population. The Blood Pressure Reduction in Danish General Practice trial: a randomized controlled parallel group trial. Family Practice 35(4): 433-439	- Study does not contain comparison relevant to this review protocol
Kostis, W. J., Cabrera, J., Lin, C. P. et al. (2020) Use of advanced statistical techniques to predict all-cause mortality in the Systolic Blood Pressure Intervention Trial. International Journal of Cardiology Hypertension 7: 100053	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Kumar, T., Robinson, T. G., Haunton, V. J. et al. (2013) The enhanced control of hypertension and thrombolysis stroke study (ENCHANTED): evaluation of low-dose rtPA and early intensive	- Conference abstract

Study	Exclusion reason
blood pressure (BP) lowering in acute ischaemic stroke. 22nd european stroke conference	
Leasure, A. C., Qureshi, A. I., Murthy, S. B. et al. (2019) Association of Intensive Blood Pressure Reduction with Risk of Hematoma Expansion in Patients with Deep Intracerebral Hemorrhage. JAMA Neurology 76(8): 949-955	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Levy, P. D., Burla, M. J., Twiner, M. J. et al. (2020) Effect of Lower Blood Pressure Goals on Left Ventricular Structure and Function in Patients With Subclinical Hypertensive Heart Disease. American Journal of Hypertension 33(9): 837-845	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Li, J., Somers, V. K., Gao, X. et al. (2021) Evaluation of Optimal Diastolic Blood Pressure Range Among Adults With Treated Systolic Blood Pressure Less Than 130 mm Hg. JAMA Network Open 4(2): e2037554	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Li, L. and Li, L. (2019) Intensive versus Usual Control of Hypertension in the Prevention of Cardiovascular and Renal Outcomes: A Cumulative Meta-Analysis of Randomized Controlled Trials. Kidney & Blood Pressure Research 44(3): 384-395	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Systematic review used as source of primary studies
Lin, M., Sameeullah, F., Meschia, J. et al. (2020) Intensive vs. standard blood pressure control in white matter disease progression: Systematic review and meta-analysis. Neurology 94(15)	- Unavailable
Magrico, R., Bigotte Vieira, M., Viegas Dias, C. et al. (2018) BP Reduction, Kidney Function Decline, and Cardiovascular Events in Patients without CKD. Clinical Journal of The American Society of Nephrology: CJASN 13(1): 73-80	- Study does not contain an intervention relevant to this review protocol: mean blood pressure target
Makin, S. and Whiteley, W. N. (2019) Intensive Blood Pressure Lowering in Patients With Renal Impairment and Lacunar Stroke. Journal of the american heart association 8(16)	- Review article but not a systematic review
Mant, J., McManus, R. J., Roalfe, A. et al. (2016) Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke--Blood Pressure) randomised controlled trial. BMJ 352: i708	- Duplicate reference
Mant, J., McManus, R. J., Roalfe, A. et al. (2016) Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention after Stroke-Blood Pressure) randomised controlled trial. BMJ (Online) 352 (no pagination)	- Duplicate reference
Mant, J., McManus, R., Roalfe, A. et al. (2014) RCT of different systolic blood pressure targets for people with a history or stroke or transient ischaemic attack: the PAST-BP (Prevention After Stroke - Blood Pressure) study. Journal of human hypertension 28: 627-628	- Conference abstract

Study	Exclusion reason
Mazighi, M., Labreuche, J., Richard, S. et al. (2020) Blood Pressure Target in Acute Stroke to Reduce HemorrhaGe After Endovascular Therapy: The Randomized BP TARGET Study Protocol. Frontiers in neurology [electronic resource]. 11: 480	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
McClure, L. A., Szychowski, J. M., Benavente, O. et al. (2016) A post hoc evaluation of a sample size re-estimation in the Secondary Prevention of Small Subcortical Strokes study. Clin Trials 13(5): 537-44	- Secondary publication of an included study that does not provide any additional relevant information
Mezue, K., Goyal, A., Pressman, G. S. et al. (2017) Blood Pressure Variability Predicts Adverse Events and Cardiovascular Outcomes in Chronic Kidney Disease: A Post-Hoc Analysis of the SPRINT Trial. American Journal of Hypertension 31(1): 48-52	- Secondary publication of an included study that does not provide any additional relevant information
Minhas, J. S., Wang, X., Lindley, R. I. et al. (2021) Comparative effects of intensive-blood pressure versus standard-blood pressure-lowering treatment in patients with severe ischemic stroke in the ENCHANTED trial. Journal of Hypertension 39(2): 280-285	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Mottl, A. K., Buse, J. B., Ismail-Beigi, F. et al. (2018) Long-Term Effects of Intensive Glycemic and Blood Pressure Control and Fenofibrate Use on Kidney Outcomes. Clinical Journal of The American Society of Nephrology: CJASN 13(11): 1693-1702	- Study does not contain an outcome relevant to this review protocol - Population not relevant to this review protocol: no subgroup data for those with established CVD
Moullaali, T. J., Wang, X., Martin, R. H. et al. (2019) Statistical analysis plan for pooled individual patient data from two landmark randomized trials (INTERACT2 and ATACH-II) of intensive blood pressure lowering treatment in acute intracerebral hemorrhage. International Journal of Stroke 14(3): 321-328	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Moullaali, T. J., Wang, X., Martin, R. H. et al. (2019) Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. Lancet Neurology 18(9): 857-864	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Myhre, P. L.; Selvaraj, S.; Solomon, S. D. (2021) Management of hypertension in heart failure with preserved ejection fraction: is there a blood pressure goal?. Current Opinion in Cardiology 36(4): 413-419	- Review article but not a systematic review
Obi, Y., Kalantar-Zadeh, K., Shintani, A. et al. (2018) Estimated glomerular filtration rate and the risk-benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial. Journal of Internal Medicine 283(3): 314-327	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Okamoto, R., Kumagai, E., Kai, H. et al. (2019) Effects of lowering diastolic blood pressure to <80 mmHg on cardiovascular mortality and	- Study does not contain comparison relevant to this review protocol

Study	Exclusion reason
events in patients with coronary artery disease: a systematic review and meta-analysis. Hypertension Research - Clinical & Experimental 42(5): 650-659	
Oparil, S., Cushman, W. C., Johnson, K. C. et al. (2018) Sprinting toward the optimal blood pressure target for hypertensive patients. Circulation Research 123(5): 531-534	- Review article but not a systematic review
Pajewski, N. M., Berlowitz, D. R., Bress, A. P. et al. (2020) Intensive vs Standard Blood Pressure Control in Adults 80 Years or Older: A Secondary Analysis of the Systolic Blood Pressure Intervention Trial. Journal of the American Geriatrics Society 68(3): 496-504	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Pareek, M., Vaduganathan, M., Biering-Sorensen, T. et al. (2019) Pulse Pressure, Cardiovascular Events, and Intensive Blood-Pressure Lowering in the Systolic Blood Pressure Intervention Trial (SPRINT). American Journal of Medicine 132(6): 733-739	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Parvar, S. L., Fitridge, R., Dawson, J. et al. (2018) Medical and lifestyle management of peripheral arterial disease. Journal of Vascular Surgery 68(5): 1595-1606	- Review article but not a systematic review
Pinho-Gomes, A. C., Azevedo, L., Copland, E. et al. (2021) Blood pressure-lowering treatment for the prevention of cardiovascular events in patients with atrial fibrillation: An individual participant data meta-analysis. PLoS Medicine / Public Library of Science 18(6): e1003599	- Study does not contain comparison relevant to this review protocol
Powers, W. J., Clarke, W. R., Grubb, R. L., Jr. et al. (2014) Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia. Neurology 82(12): 1027-32	- Study design not relevant to this review protocol: non-randomised
Qureshi, A. I., Foster, L. D., Lobanova, I. et al. (2020) Intensive Blood Pressure Lowering in Patients with Moderate to Severe Grade Acute Cerebral Hemorrhage: Post Hoc Analysis of Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 Trial. Cerebrovascular Diseases 49(3): 244-252	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Qureshi, A. I., Huang, W., Lobanova, I. et al. (2020) Outcomes of Intensive Systolic Blood Pressure Reduction in Patients With Intracerebral Hemorrhage and Excessively High Initial Systolic Blood Pressure: Post Hoc Analysis of a Randomized Clinical Trial. JAMA Neurology 77(11): 1355-1365	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Qureshi, A. I., Huang, W., Lobanova, I. et al. (2020) Systolic Blood Pressure Reduction and Acute Kidney Injury in Intracerebral Hemorrhage. Stroke 51(10): 3030-3038	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol - Study design not relevant to this review protocol: treatment received for <1 year

Study	Exclusion reason
Qureshi, A. I., Palesch, Y. Y., Foster, L. D. et al. (2018) Blood Pressure-Attained Analysis of ATACH 2 Trial. Stroke 49(6): 1412-1418	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol - Population not relevant to this review protocol: no subgroup data for those with established CVD
Rao, S., Segar, M. W., Bress, A. P. et al. (2020) Association of Genetic West African Ancestry, Blood Pressure Response to Therapy, and Cardiovascular Risk Among Self-Reported Black Individuals in the Systolic Blood Pressure Reduction Intervention Trial (SPRINT). JAMA Cardiology 13: 13	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Robinson, T. G. and Anderson, C. S. (2014) The ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED): evaluation of low-dose rtPA and early intensive blood pressure (BP) lowering in acute ischaemic stroke. European stroke conference 2014	- Conference abstract
Robinson, T. G.; Haunton, V. J.; Anderson, C. S. (2013) The ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED): evaluation of low-dose rtPA and early intensive blood pressure (BP) lowering in acute ischaemic stroke. 8th UK stroke forum conference: 80	- Conference abstract
Rocco, M. V., Sink, K. M., Lovato, L. C. et al. (2018) Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT). American Journal of Kidney Diseases 71(3): 352-361	- Secondary publication of an included study that does not provide any additional relevant information
Rodriquez, M. (2018) Intensive Treatment of Blood Pressure in Acute Ischemic Stroke. Study TICA 2 (TICA).	- Conference abstract
Rosendorff, C. and Black, H. R. (2009) Evidence for a lower target blood pressure for people with heart disease. Current Opinion in Cardiology 24(4): 318-24	- Review article but not a systematic review
Rostomian, A. H., Tang, M. C., Soverow, J. et al. (2020) Heterogeneity of treatment effect in SPRINT by age and baseline comorbidities: The greatest impact of intensive blood pressure treatment is observed among younger patients without CKD or CVD and in older patients with CKD or CVD. Journal of Clinical Hypertension 22(9): 1723-1726	- Secondary publication of an included study that does not provide any additional relevant information
Roush, G. C., Zubair, A., Singh, K. et al. (2019) Does the benefit from treating to lower blood pressure targets vary with age? A systematic review and meta-analysis. Journal of Hypertension 37(8): 1558-1566	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Rueda-Ochoa, O. L., Rojas, L. Z., Ahmad, S. et al. (2019) Impact of cumulative SBP and serious adverse events on efficacy of intensive blood	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
pressure treatment: a randomized clinical trial. Journal of Hypertension 37(5): 1058-1069	
Salomon, L. (2018) Blood pressure target in acute stroke to reduce hemorrhage after endovascular therapy (BP-TARGET).	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Shapiro, B. P., Ambrosius, W. T., Blackshear, J. L. et al. (2018) Impact of Intensive Versus Standard Blood Pressure Management by Tertiles of Blood Pressure in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension 71(6): 1064-1074	- Secondary publication of an included study that does not provide any additional relevant information
Sharma, V. K., Tan, B. Y. Q., Sim, M. Y. et al. (2018) Rationale and design of a randomized trial of early intensive blood pressure lowering on cerebral perfusion parameters in thrombolysed acute ischemic stroke patients. Medicine (United States) 97 (40)	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Sheibani, N., Wong, K. H., Turan, T. N. et al. (2021) White Matter Hyperintensity and Cardiovascular Disease Outcomes in the SPRINT MIND Trial. Journal of Stroke & Cerebrovascular Diseases 30(6): 105764	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Shimada, K. (2018) A large-scale clinical study to investigate the secondary preventive effect of strict antihypertensive therapy in patients with a previous history of stroke.	- Unavailable
Singleton, M. J., Chen, L. Y., Whalen, S. P. et al. (2020) Effect of intensive blood pressure lowering on incident atrial fibrillation: A systematic review and meta-analysis. Journal of Atrial Fibrillation 13(4): 28-33	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Sink, K. M., Evans, G. W., Shorr, R. I. et al. (2018) Syncope, Hypotension, and Falls in the Treatment of Hypertension: Results from the Randomized Clinical Systolic Blood Pressure Intervention Trial. Journal of the American Geriatrics Society 66(4): 679-686	- Study does not contain comparison relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Sobieraj, P., Lewandowski, J., Sinski, M. et al. (2019) Determination of optimal on-treatment diastolic blood pressure range using automated measurements in subjects with cardiovascular disease-Analysis of a SPRINT trial subpopulation. Journal of Clinical Hypertension 21(7): 911-918	- Study does not contain comparison relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Sobieraj, P., Lewandowski, J., Sinski, M. et al. (2019) Low Diastolic Blood Pressure is Not Related to Risk of First Episode of Stroke in a High-Risk Population: A Secondary Analysis of SPRINT. Journal of the American Heart Association 8(4): e010811	- Study does not contain comparison relevant to this review protocol - Secondary publication of an included study that does not provide any additional relevant information
Takami, Y., Yamamoto, K., Arima, H. et al. (2019) Target blood pressure level for the treatment of elderly hypertensive patients: a systematic review and meta-analysis of randomized trials. Hypertension Research - Clinical & Experimental 42(5): 660-668	- Population not relevant to this review protocol: no subgroup data for those with established CVD

Study	Exclusion reason
Tanaka, K., Jujo, K., Yamaguchi, J. et al. (2019) Optimal Blood Pressure in Patients With Coronary Artery Disease and Chronic Kidney Disease: HIJ-CREATE Substudy. American Journal of the Medical Sciences 358(3): 219-226	- Study does not contain comparison relevant to this review protocol
Togashi, K., Joffe, A. M., Sekhar, L. et al. (2015) Randomized pilot trial of intensive management of blood pressure or volume expansion in subarachnoid hemorrhage (IMPROVES). Neurosurgery 76(2): 125-34; discussion 134	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Tsujimoto, T. and Kajio, H. (2019) Intensive Blood Pressure Treatment for Resistant Hypertension: Secondary Analysis of a Randomized Controlled Trial. Hypertension 73(2): 415-423	- Secondary publication of an included study that does not provide any additional relevant information
Vaduganathan, M., Pareek, M., Kristensen, A. M. D. et al. (2021) Prevention of heart failure events with intensive versus standard blood pressure lowering across the spectrum of kidney function and albuminuria: a SPRINT substudy. European Journal of Heart Failure 23(3): 384-392	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Wakabayashi, M.; Yamada, T.; Yamada, T. (2020) Intensive blood pressure control and fall injuries in older adults: A systematic review and meta-analysis. J. Am. Soc. Nephrol. 31: 533-None	- Unavailable
Wang, J., Chen, Y., Xu, W. et al. (2019) Effects of intensive blood pressure lowering on mortality and cardiovascular and renal outcomes in type 2 diabetic patients: A meta-analysis. PLoS ONE [Electronic Resource] 14(4): e0215362	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol
Wang, X., Sandset, E. C., Moullaali, T. J. et al. (2019) Determinants of the high admission blood pressure in mild-to-moderate acute intracerebral hemorrhage. Journal of Hypertension 37(7): 1463-1466	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol
White, H. D., Stewart, R. A. H., Dalby, A. J. et al. (2020) In patients with stable coronary heart disease, low-density lipoprotein-cholesterol levels < 70 mg/dL and glycosylated hemoglobin A1c <7% are associated with lower major cardiovascular events: Targets and cardiovascular events. American Heart Journal 225: 97-107	- Study does not contain comparison relevant to this review protocol
White, W. B., Jalil, F., Cushman, W. C. et al. (2018) Average Clinician-Measured Blood Pressures and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Ischemic Heart Disease in the EXAMINE Trial. Journal of the American Heart Association 7(20): e009114	- Study does not contain comparison relevant to this review protocol

Study	Exclusion reason
White, W. B., Marfatia, R., Schmidt, J. et al. (2013) INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINe in the ElderlY (INFINITY). Am Heart J 165(3): 258-265.e1	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol - Study does not contain an intervention relevant to this review protocol: mean blood pressure target
White, W. B., Wakefield, D. B., Moscufo, N. et al. (2019) Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY). Circulation 140(20): 1626-1635	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Williamson, J. D., Supiano, M. A., Applegate, W. B. et al. (2016) Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >75 years a randomized clinical trial. JAMA - journal of the american medical association 315(24): 2673-2682	- Duplicate reference
Williamson, J. D., Supiano, M. A., Applegate, W. B. et al. (2016) Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: a Randomized Clinical Trial. Jama 315(24): 2673-2682	- Duplicate reference
Williamson, J. D., Supiano, M. A., Applegate, W. B. et al. (2016) Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. Jama 315(24): 2673-82	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Williamson, J. D., Supiano, M. A., Applegate, W. B. et al. (2016 Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >=75 Years: A Randomized Clinical Trial. JAMA 315(24): 2673-82	- Duplicate reference
Wright, C. B., Auchus, A. P., Lerner, A. et al. (2021) Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes. Hypertension (dallas, tex. : 1979) 77(4): 1391-1398	- Secondary publication of an included study that does not provide any additional relevant information
Wu, W., Liu, J., Li, A. et al. (2019) Effect of Intensive Blood Pressure Control on Carotid Morphology and Hemodynamics in Chinese Patients with Hyperhomocysteinemia-Type Hypertension and High Risk of Stroke. Medical Science Monitor 25: 5717-5726	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Xu, T., Zhang, Y., Bu, X. et al. (2017) Blood pressure reduction in acute ischemic stroke according to time to treatment: a subgroup analysis of the China Antihypertensive Trial in Acute Ischemic Stroke trial. Journal of Hypertension 35(6): 1244-1251	- Comparator in study does not match that specified in this review protocol

Study	Exclusion reason
Yang, D. Y., Nie, Z. Q., Liao, L. Z. et al. (2019) Phenomapping of subgroups in hypertensive patients using unsupervised data-driven cluster analysis: An exploratory study of the SPRINT trial. European Journal of Preventive Cardiology 26(16): 1693-1706	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Secondary publication of an included study that does not provide any additional relevant information
Yang, J., Song, L., Li, G. et al. (2019) Intensive ambulance-delivered blood pressure reduction in hyper-acute stroke trial. Cerebrovascular diseases (Basel, Switzerland) 48(suppl1): 111	- Study does not contain comparison relevant to this review protocol
Ye, Z., Ai, X., Zheng, J. et al. (2017) Antihypertensive treatments for spontaneous intracerebral hemorrhage in patients with cerebrovascular stenosis: A randomized clinical trial (ATICHST). Medicine 96(26): e7289	- Study does not contain an outcome relevant to this review : Trial protocol only
You, S., Wang, X., Lindley, R. I. et al. (2017) Early Cognitive Impairment after Intracerebral Hemorrhage in the INTERACT1 Study. Cerebrovascular Diseases 44(56): 320-324	- Population not relevant to this review protocol: no subgroup data for those with established CVD - Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Zanchetti, A., Hansson, L., Clement, D. et al. (2003) Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers?. J Hypertens 21(4): 797-804	- Secondary publication of an included study that does not provide any additional relevant information
Zanchetti, A., Hansson, L., Dahlöf, B. et al. (2001) Effects of individual risk factors on the incidence of cardiovascular events in the treated hypertensive patients of the Hypertension Optimal Treatment Study. HOT Study Group. J Hypertens 19(6): 1149-59	- More recent systematic review included that covers the same topic - Systematic review used as source of primary studies
Zanchetti, A., Liu, L., Mancia, G. et al. (2014) Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. Journal of Hypertension 32(9): 1888-97	- Trial protocol only: full results not published
Zang, J., Liang, J., Zhuang, X. et al. (2021) Intensive blood pressure treatment in coronary artery disease: implications from the Systolic Blood Pressure Intervention Trial (SPRINT). Journal of Human Hypertension 15: 15	- Secondary publication of an included study that does not provide any additional relevant information
Zhang W, Zhang S, Deng Y et al. (2021) Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. The New England journal of medicine	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Zhang, L., Sun, X., Liao, L. et al. (2019) Effectiveness of blood pressure-lowering treatment by the levels of baseline Framingham risk score: A post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT).	- Population not relevant to this review protocol: no subgroup data for those with established CVD

Study	Exclusion reason
Journal of Clinical Hypertension 21(12): 1813-1820	- Secondary publication of an included study that does not provide any additional relevant information
Zhang, S., Wu, S., Ren, J. et al. (2020) Strategy of blood pressure intervention in the elderly hypertensive patients (STEP): Rational, design, and baseline characteristics for the main trial. Contemporary Clinical Trials 89: 105913	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol - Population not relevant to this review protocol: no subgroup data for those with established CVD
Zhang, Y., Liang, M., Sun, C. et al. (2019) Effect of intensive lowering of systolic blood pressure treatment on heart failure events: a meta-analysis of randomized controlled studies. Journal of Human Hypertension 33(9): 648-657	- Population not relevant to this review protocol: no subgroup data for those with established CVD
Zhou, J. C., Zhang, N., Zhang, Z. H. et al. (2017) Intensive blood pressure control in patients with acute type B aortic dissection (RAID): study protocol for randomized controlled trial. Journal of Thoracic Disease 9(5): 1369-1374	- Study does not contain an outcome relevant to this review: Trial protocol only
Zhou, Z., Xia, C., Carcel, C. et al. (2021) Intensive versus guideline-recommended blood pressure reduction in acute lacunar stroke with intravenous thrombolysis therapy: The ENCHANTED trial. European Journal of Neurology 28(3): 783-793	- Study does not contain comparison relevant to this review protocol: blood pressure target thresholds do not match this protocol
Zonneveld, Tp, Richard, E, Vergouwen, Mdi et al. (2018) Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database of Systematic Reviews	- Study does not contain comparison relevant to this review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 14: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix K – Research recommendations – full details

K.1 Research recommendation

The following research recommendation is an amendment to that which was previously published in NG136 in 2019.

What is the optimum blood pressure target in adults aged 80 and over with treated primary hypertension, with or without established cardiovascular disease?

K.1.1 Why this is important

Stroke and heart failure are major causes of mortality and morbidity in older people. These conditions can result in loss of independence and a severe reduction in quality of life. A major modifiable risk factor for both stroke and heart failure is hypertension, and evidence exists to show that drug treatment can reduce rates of death from stroke and heart failure in selected older populations. However, considerable observational data confirms a U-shaped relationship between blood pressure and mortality specifically in people aged 80 and over, with an increasing risk of mortality being seen at both lower and higher blood pressure values around an optimal value that confers the minimum mortality risk. Older people are also particularly prone to the potential side effects of antihypertensive medication. There is a need, therefore, to find the optimal balance between lowering blood pressure with medication and the frequency with which adverse reaction to medication occurs. How intensive should blood pressure treatment in the older person be, and how should treatment targets be modified in those living with frailty?

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Evidence indicates that in selected older people treating to a target blood pressure of below 150/90 mmHg reduces the rate of all-cause mortality, stroke and heart failure with an acceptable rate of adverse reaction to medication. A recent study suggested that there might be additional benefit to treating to a lower target. However, the positive results seen in selected populations may not be replicated when the same treatments are applied to those who are at higher risk of adverse effects of medication, or those with established cardiovascular disease.
Relevance to NICE guidance	Evidence on treating to a lower blood pressure target in people aged over 80 would inform future updates of this guidance. Current guidance recommends a lower blood pressure target for people aged under 80 or below 140/90 mmHg, as evidence is lacking for more intensive treatment in those aged 80 and over, especially. Current guidance recommends a target of below 150/90 mmHg in those aged 80 and over.
Relevance to the NHS	There is the potential to reduce mortality and morbidity in people aged 80 and over. This could in turn result in cost savings.
National priorities	This is consistent with the National Service Framework for Older People

Current evidence base	No studies in people with CVD comparing more intensive targets to less intensive targets looked specifically at people aged over 80. Further research is therefore required to determine if the benefits of intensive treatment outweigh the risks for this group in UK general practice.
Equality considerations	Older adults living with frailty are more at risk of adverse reaction to antihypertensive agents and therefore need special consideration.

K.1.3 Modified PICO table

Population	People aged 80 and over diagnosed with hypertension with or without established cardiovascular disease (past medical history of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, aortic aneurysm or heart failure). (Including the following subgroups: presence or absence of established cardiovascular disease, presence or absence of frailty (Clinical Frailty Scale: level 5 and above), cognitive impairment, or low diastolic BP at baseline).
Intervention	Treatment of hypertension to a target blood pressure of below 140/90 mmHg as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 135/85 mmHg.
Comparator	Treatment of hypertension to a target blood pressure of below 150/90 mmHg as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 145/85 mmHg.
Outcome	All-cause mortality, stroke (ischaemic or haemorrhagic), myocardial infarction, hospitalisation due to angina, heart failure, acute kidney injury, falls, discontinuation of antihypertensive agents due to side-effects, comparison of health-related quality of life and cost effectiveness.
Study design	Randomised clinical trial (RCT)
Timeframe	Medium- to long-term (minimum 12 months)
Additional information	None

K.2 Research recommendation

What are the optimal blood pressure targets in adults with hypertension and aortic aneurysm, and does this vary by age?

K.2.1 Why this is important

Abdominal aortic aneurysm (AAA) is found in 4-8% of individuals undergoing screening studies and has a complex pathophysiology. There are consistent data linking hypertension with an increased risk of aneurysm rupture. Evidence to determine the optimum blood pressure in order to reduce risk of rupture is lacking. Thoracic aortic aneurysm (TAA) occurs in approximately 0.5-1% of the population (depending on definition) and the majority of these individuals are also hypertensive. Systolic hypertension appears to correlate with both aneurysm expansion and the development of acute aortic syndrome. Evidence regarding the optimum level of blood pressure control in patients with a diagnosis of TAA is lacking.

K.2.2 Rationale for research recommendation

Importance to ‘patients’ or the population	An increased focus on the management of hypertension in patients with a concomitant diagnosis of AAA or TAA. This could involve an

	increase in the number of anti-hypertensive therapies required to achieve adequate control and an increase frequency of blood pressure monitoring.
Relevance to NICE guidance	Aortic aneurysm has been considered in this guideline under the CVD umbrella but there is a lack of data on optimal blood pressure targets in this group. Evidence on treating to a lower blood pressure target in people with aortic aneurysm would inform future updates of this guidance. Current guidance recommends a lower blood pressure target for people aged under 80 or below 140/90 mmHg, and a target of below 150/90 mmHg in those aged 80 and over.
Relevance to the NHS	Increased focus on hypertension management in patients with AAA/TAA. However, as hypertension management and services are already embedded this should not be logistically impactful.
National priorities	Improving outcomes for patients with cardiovascular disease is central to the NHS long-term plan.
Current evidence base	No studies comparing more intensive targets to less intensive targets in adults with aortic aneurysm were identified. Further research is therefore required to determine if the benefits of intensive treatment outweigh the risks for this group.
Equality considerations	None known

K.2.3 Modified PICO table

Population	Inclusion: Adults diagnosed with hypertension and aortic aneurysm (AAA or TAA) under active surveillance. Exclusion: adults with repaired aortic aneurysm (post-surgical or post-endovascular repair).
Intervention	Treatment of hypertension to a target blood pressure of below 130/80 mmHg in those aged <80 years or 140/80 mmHg in those aged ≥80 years as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 125/75 mmHg or 135/75 mmHg for those aged <80 and ≥80 years, respectively.
Comparator	Treatment of hypertension to a target blood pressure of below 140/90 mmHg in those aged <80 years or 150/90 mmHg in those aged ≥80 years as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 135/85 mmHg or 145/85 mmHg for those aged <80 and ≥80 years, respectively.
Outcome	All-cause mortality, stroke (ischaemic or haemorrhagic), myocardial infarction, rate of aneurysm expansion, aneurysm rupture, development of acute aortic syndrome, hospitalisation due heart failure, acute kidney injury, falls, discontinuation of antihypertensive agents due to side-effects, comparison of health-related quality of life and cost effectiveness.
Study design	Randomised clinical trial (RCT)
Timeframe	Long-term (minimum 3 years)

Additional information	None

K.3 Research recommendation

What are the optimal blood pressure targets in adults with prior ischaemic or haemorrhagic stroke and does this vary by age?

K.3.1 Why this is important

Stroke is a major cause of mortality and morbidity, especially in older people, and can result in loss of independence and a severe reduction in quality of life. A major modifiable risk factor for stroke is hypertension. Evidence exists to show that hypertension is related to stroke in a log-linear fashion, such that any given absolute difference in baseline blood pressure is associated with a similar relative risk reduction of stroke at all blood pressure values, down to approximately 115 mmHg systolic blood pressure. This relationship holds true for both ischaemic strokes and for primary intracerebral haemorrhages. However, only limited evidence is available on the optimal blood pressure targets for people with hypertension and a history of stroke. Since antihypertensive medication has potential side effects, there is a need for data to inform the optimal balance between the benefits of lowering blood pressure with medication, including reduced recurrent stroke incidence, and the frequency with which adverse reaction to medication occurs. It is also important to have data specifically in those aged 80 or over, in whom the current blood pressure target is higher, with an aim to achieve values below 150/90 mmHg. These patients are at highest risk of recurrent stroke by virtue of their age and comorbidities and so, if tolerated, could have more to gain from lower blood pressure targets in terms of reduced stroke recurrence.

K.3.2 Rationale for research recommendation

Importance to ‘patients’ or the population	If demonstrated that treating to a lower target blood pressure was beneficial in terms of reduced risk of cardiovascular events, and also safely tolerated, treating to a lower target in adults with prior stroke could reduce the incidence and prevalence of recurrent stroke, which would greatly improve the quality of life for those surviving a stroke, and their carers.
Relevance to NICE guidance	Limited evidence suggested a possible benefit of lower blood pressure targets for people with prior stroke. However, the evidence was insufficient to support a recommendation. Therefore, new evidence would inform future updates of this guidance. Current guidance recommends a lower blood pressure target for people aged under 80 or below 140/90 mmHg, and a target of below 150/90 mmHg in those aged 80 and over.
Relevance to the NHS	There is the potential to reduce mortality and morbidity in people with prior stroke. This could in turn result in cost savings. Not only is stroke common, it also requires an inpatient stay and around 10-15% of those patients admitted need to be discharged to institutional care.
National priorities	Improving outcomes for patients with cardiovascular disease is central to the NHS long-term plan.

Current evidence base	Four RCTs assessing lower versus standard blood pressure targets in people with prior stroke or TIA were identified. This evidence suggested a possible benefit for reduced recurrent stroke in those treated to a lower blood pressure target. However, there was insufficient evidence on the possible harms and the evidence was considered too limited in quantity and quality to inform a recommendation.
Equality considerations	This research area addresses age- and disability-related equality considerations. Adults who have had a prior stroke have an increased likelihood of having an existing disability or are older.

K.3.3 Modified PICO table

Population	Adults diagnosed with hypertension and with a history of stroke (ischaemic or primary intracerebral haemorrhage). Stratified by age: <80 years and ≥80 years and by type of stroke (ischaemic or haemorrhagic).
Intervention	Treatment of hypertension to a target blood pressure of below 130/80 mmHg as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 125/75 mmHg.
Comparator	Treatment of hypertension to a target blood pressure of below 140/90 mmHg in those aged <80 years or 150/90 mmHg in those aged ≥80 years as measured in the UK general practice clinical setting or a home or ambulatory blood pressure target of below 135/85 mmHg or 145/85 mmHg for those aged <80 and ≥80 years, respectively.
Outcome	All-cause mortality, recurrent stroke or TIA, myocardial infarction, hospitalisation due to heart failure, acute kidney injury, falls, discontinuation of antihypertensive agents due to side-effects,health-related quality of life and cost effectiveness.
Study design	Randomised controlled trial
Timeframe	Medium- to long-term (minimum 12 months)
Additional information	Consider using a defined drug regime as there could be differences in benefits with different classes of drugs. Consider how de-escalation would be managed (if at all) if blood pressure falls below certain limits.