National Institute for Health and Care Excellence

Final

Hypertension in adults: diagnosis and management

[C] Evidence review for initiating treatment

NICE guideline NG136

Intervention evidence review underpinning recommendations 1.4.9 to 1.4.14 in the guideline

August 2019

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: At what blood pressure and/or cardiovascular disease risk threshold should antihypertensive drug treatment be initiated for adults with hypertension?

1.2 Introduction

Blood pressure varies across the population, and there is no natural cut-off point above which 'hypertension' definitively exists and below which it is does not. The threshold at which treatment should be initiated is therefore based on a risk or benefit calculation.

The current UK recommendations for initiating antihypertensive treatment are based on a combination of blood pressure levels and cardiovascular disease risk thresholds. Specifically, in individuals with stage 1 hypertension (clinic blood pressure 140/90 to 159/99 mmHg) antihypertensive treatment is only recommended if an individual's 10-year risk for cardiovascular events is greater than 20%. This 2-step process for deciding when to initiate treatment has the potential to result in confusion and contrasts to the recently published lipid guideline in which treatment initiation is based on the cardiovascular disease risk threshold. In this chapter, the evidence for initiating treatment based on blood pressure (BP) or cardiovascular disease (CVD) risk thresholds is evaluated.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	At what blood pressure and/or cardiovascular disease risk threshold should antihypertensive drug treatment be initiated for adults with hypertension?
Intervention(s)	Treatment initiation at different thresholds
Comparison(s)	Compared against each other (comparing different blood pressure and/or cardiovascular risk thresholds) Also within each other
Outcomes	Assessed at 12 months or more (using final endpoint) **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • Heart failure needing hospitalisation • Vascular procedures (including both coronary and carotid artery procedures) • Angina needing hospitalisation • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Changes in estimated Glomerular filtration rate (eGFR) or creatinine • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke

	data] • [Coronary heart disease outcome in the absence of MI data]
Study design	Systematic reviews (SR), randomised control trials (RCT), Non-randomised study (NRS)

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[134] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

One individual patient data (IPD) meta-analysis,[162] 1 longitudinal cohort study[155] and 2 systematic reviews were included in the review;[41, 107] these are summarised below (Table 2). Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

Risk of bias of the studies included in the IPD meta-analysis and systematic reviews had been measured using the Cochrane risk of bias tool, which we incorporated into our GRADE assessment for overall quality assessment per outcome. Where risk of bias assessments were available for some, but not all, studies included within one of the systematic reviews, additional risk of bias assessments were conducted and integrated with the existing assessments per outcome, as per section 2.3.4.1 of the methods chapter. Where risk of bias was not available for the studies included within one of the systematic reviews, the ROBIS checklist was incorporated into the GRADE assessments for overall quality assessment per outcome.

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.

1.5.2 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Brunström 2018[41] (systematic review of RCTs)	Systolic blood pressure thresholds: <140 (n=68,966) 140–159 (n=43,889) ≥160 mmHg (n=79,940) Treatment versus no treatment	Adults with hypertension, with and without diabetes (n=192,795)	At 4 years: All-cause mortality Stroke Coronary heart disease Heart failure	Study downgraded for very serious indirectness as the population included coronary artery disease (CAD), mixed CVD and post-stroke. Also, the review included studies that pooled low intensity treatment and no treatment arms (16% of study population).
Law 2009[107] (systematic review of RCTs and non-randomised studies)	Diastolic blood pressure thresholds: >80 (n=42,599) 80–84 (n=37,516) 85–89 (n=39,731) 90–94 (n=38,646) >95 (n=6,195) Treatment versus no treatment.	Adults with hypertension, with and without diabetes (n=464,000; multiple comparisons, actual number of participants included within the diastolic thresholds analysis: n=164,687)	At 4 years: Stroke Coronary heart disease	Study downgraded for very serious indirectness as the population included CAD, mixed CVD and post-stroke. Also, review included studies that pooled low intensity treatment and no treatment arms.
Sheppard 2018[155] (cohort study)	Systolic blood pressure threshold of 140–159 mmHg with a low cardiovascular risk (mean cardiovascular risk threshold of 8%; QRISK2) Treatment versus no treatment	Adults with hypertension, without diabetes (n=38,286)	At 5.8 years: Mortality Stroke Heart failure MI Non-MI acute coronary syndrome Hypotension Acute Kidney Injury	Participants with previous cardiovascular events were excluded from the trial 7,720 participants (20.2%) included in the main analysis had a previous risk score recorded, and an additional 9,096 (23.8%) had available risk factor information to calculate a QRISK2 score. For the remaining 21,050 (56%), cardiovascular risk

Study	Intervention and comparison	Population	Outcomes	Comments
				was estimated by inserting age- and sex-standardised mean cholesterol values and Townsend scores from the Health Survey for England into the algorithm to replace missing data. Downgraded for indirectness because 41.6% of the non-treatment arm were on treatment at some point in the trial. Some QRISK2 inputs were also not available in all participants and were imputed (estimated 56% of the population had some form of imputation). The mean diastolic blood pressure was also 88.5 (standard deviation [SD] 5.2) mmHg, which is less than the diastolic threshold for stage 1 hypertension.
Sundstrom 2015[162] (IPD)	Systolic blood pressure threshold of 140–159 mmHg Treatment versus no treatment	Adults with hypertension and type 2 diabetes (n=6361)	At 4.4 years: All-cause mortality Stroke Heart failure	RCTs where at least 80% of participants had grade 1 hypertension and had no previous cardiovascular disease were included. To note that risk of bias for individual studies included within the review was not available. The ROBIS checklist (assessing the quality of the systematic review itself) was therefore incorporated into the GRADE assessments for overall quality assessment per outcome.

See appendix D for full evidence tables.

1.5.3 Excluded studies

There were 4 systematic reviews using individual patient data (IPD) identified for this review. IPDs would be preferentially included over other systematic reviews if directly relevant to the review protocol, as they use raw data from each participant across all the included trials as opposed to summary data. However, due to substantial deviations from the protocol for this review, 3 of these IPDs were excluded, as were 3 systematic reviews (see table below for detailed exclusion reasons).

Table 3: Excluded reviews

Systematic review	Exclusion reasons
Blood Pressure Lowering Trialists Collaboration IPD 2014[163]	• The study used a customised risk calculator to stratify participants into risk groups. It was unclear how risk was calculated and whether the groups were similar to validated risk tools such as Framingham, QRISK2 or 3. The risk calculator also used previous cardiovascular events, which is not considered a useful measure and is not included in any validated risk tools. • The cardiovascular risk groups compared within each category also differed within each outcome, which made results difficult to interpret. • The population didn't match this review protocol's requirements: unclear if participants were already treated or on other treatment (55.9% had previous treatment) and unclear if baseline cardiovascular risk was measured while participants were untreated. 39.1% of the population had diabetes with no detail of whether this was type 1 or type 2 diabetes. • Pooled trial data of 'less intensive arms' with placebo, which was an exclusion criterion on the protocol for this review. • No minimum trial duration inclusion criterion, whereas this review had a requirement of trials with a minimum duration of 12 months. • The trialists used meta-regression with the observed 5-year risks to extend all results to 5 years; the average follow up time was not stated.
Blood Pressure Lowering Trialists Collaboration IPD 2011[50]	• For the blood pressure categories outlined in the protocol for this review, the only available outcome was major cardiovascular events. This composite outcome was included in the review protocol but was only to be included if individual cardiovascular event outcomes were not available. This is because these outcomes were considered to be more informative. • Individual morbidity and mortality outcomes were given at systolic blood pressure thresholds of above 140 mmHg and below 140 mmHg. Above 140 mmHg was not a threshold listed in the protocol and would not have informed recommendations as this encompasses stage 1 and stage 2 hypertension. The below 140 mmHg comparison was considered for inclusion but 58.9% had other cardiovascular disease and were taking medication for secondary prevention.

Systematic review	Exclusion reasons
	• Baseline characteristics were not stated, and the IPD included participants that were already treated; it was unclear if baseline blood pressure had been measured while participants were untreated.
Asayama 2009 IPD[17]	• Study carried out in Japan and considered not to be applicable to the UK population due to the known differences in antihypertensive treatment and prevalence of cardiovascular events, that is, different antihypertensive drugs administered and lower dosages of treatment given than in the UK. The prevalence of stroke and heart failure are higher in Japan, which were the only included outcomes in the IPD. In addition, the incidence of myocardial infarction tends to be lower in Japanese people with hypertension, which is an outcome of interest for this guideline. • The comparisons included were not in line with this review protocol. Rather than comparing treatment versus no treatment at each blood pressure threshold, the IPD compared treatment at each threshold versus no treatment in the 'optimal' below 120 mmHg systolic blood pressure category. This would have substantially influenced the results. • Unclear from the IPD whether baseline blood pressure was measured before treatment was initiated.
Brunström 2016[40]	• There is an overlap in included studies included in this review with those included in Sundstrom 2015.[162] The IPD (Sundstrom) was therefore preferentially included.
Emdin 2005[55]	• There is an overlap in included studies included in this review with those included in Sundstrom 2015.[162] The IPD (Sundstrom) was therefore preferentially included. • Stratified by above 140 mmHg and below 140 mmHg; above 140 mmHg was not a threshold listed in the protocol and would not have informed recommendations as this encompasses stage 1 and stage 2 hypertension. 65% of the population in the below 140 mmHg threshold had other cardiovascular disease and were taking antihypertensive medication for secondary prevention
Ettehad 2016[57]	• Majority of participants had coronary heart disease and 15–40% had heart failure, which were not included in this review.

See the full excluded studies list in appendix I. Table 26 outlines the full excluded studies list, and Table 25 provides additional detail of studies that were included in the previous guideline iteration (CG127) but excluded from this update.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Treatment versus no treatment at systolic blood pressure thresholds (with and without type 2 diabetes)

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with Control	Risk difference with Treatment versus no treatment (95% CI)
All-cause mortality <140 mmHg	68,816 (1 study) 4 years	LOW[1] due to indirectness	RR 0.98 (0.9 to 1.07)		[4,897 events in 68,816 people][5]
All-cause mortality 140–159 mmHg	41,049 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.87 (0.75 to 1.01)	56 per 1,000[3]	7 fewer per 1,000 (from 14 fewer to 1 more)
All-cause mortality ≥160 mmHg	79,900 (1 study) 4 years	LOW[1] due to indirectness	RR 0.93 (0.87 to 0.99)	81 per 1,000[3]	6 fewer per 1,000 (from 1 fewer to 11 fewer)
Stroke <140 mmHg	62,751 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.85 (0.68 to 1.06)	30 per 1,000[4]	4 fewer per 1,000 (from 10 fewer to 2 more)
Stroke 140–159 mmHg	41,641 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.86 (0.72 to 1.03)	42 per 1,000[4]	6 fewer per 1,000 (from 12 fewer to 1 more)
Stroke ≥160 mmHg	79,900 (1 study) 4 years	LOW[1] due to indirectness	RR 0.69 (0.6 to 0.79)	62 per 1,000[4]	19 fewer per 1,000 (from 13 fewer to 25 fewer)
Coronary heart disease <140 mmHg	62,617 (1 study) 4 years	LOW[1] due to indirectness	RR 0.98 (0.88 to 1.09)	66 per 1,000[4]	1 fewer per 1,000 (from 8 fewer to 6 more)
Coronary heart disease 140–159 mmHg	42,543 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.86 (0.76 to 0.97)	34 per 1,000[4]	5 fewer per 1,000 (from 1 fewer to 8 fewer)
Coronary heart disease ≥160 mmHg	78,617 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.86 (0.78 to 0.95)	56 per 1,0,00[4]	12 fewer per 1,000 (from 8 fewer to 15 fewer)
Heart failure <140 mmHg	60,879 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.88 (0.78 to 0.99)	Moderate	[2,261 events in 60,879 people] [5]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Treatment versus no treatment (95% CI)
Heart failure 140–159 mmHg	35,254 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.87 (0.73 to 1.04)	Moderate	[1,113 events in 35,254 people][5]
Heart failure ≥160 mmHg	23,395 (1 study) 4 years	LOW[1] due to indirectness	RR 0.53 (0.42 to 0.67)	Moderate	[520 events in 23,395 people][5]

[1]Downgraded by 1 increment due to population or outcome indirectness or by 2 increments for both population and outcome indirectness
[2]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3]Control group risk not reported; values extrapolated from Bulpitt 1988[43]
[4]Control group risk not reported; values extrapolated from Law 2009[107]
[5]Control group risk not reported; therefore, absolute risk could not be calculated: no data was available that values could be extrapolated from.

Table 5: Clinical evidence summary: Treatment versus no treatment at systolic blood pressure thresholds (type 2 diabetes)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment (diabetes)	Risk difference with Treatment (95% CI)
All-cause mortality 140–159 mmHg	6,334 (1 study) 4.4 years	MODERATE[1] due to imprecision	RR 0.76 (0.64 to 0.9)	90 per 1,000	22 fewer per 1,000 (from 9 fewer to 32 fewer)
Stroke 140–159 mmHg	5,897 (1 study) 4.4 years	MODERATE[1] due to imprecision	RR 0.8 (0.68 to 0.95)	94 per 1,000	19 fewer per 1,000 (from 5 fewer to 30 fewer)
Heart failure 140–159 mmHg	5,629 (1 study) 4.4 years	MODERATE1 due to imprecision	RR 0.78 (0.56 to 1.09)	28 per 1,000	6 fewer per 1,000 (from 12 fewer to 2 more)

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence summary: Effects of treatment versus no treatment at diastolic blood pressure thresholds (with and without type 2 diabetes)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Treatment versus no treatment (95% CI)
Stroke <80 mmHg	42,599 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.74 (0.68 to 0.82)	45 per 1,000	12 fewer per 1,000 (from 8 fewer to 15 fewer)
Stroke 80–84 mmHg	37,516 (1 study) 4 years	VERY LOW[1,2] due to indirectness, imprecision	RR 0.76 (0.67 to 0.87)	28 per 1,000	7 fewer per 1,000 (from 4 fewer to 9 fewer)
Stroke 85–89 mmHg	39,731 (1 study) 4 years	LOW[1] due to indirectness	RR 0.68 (0.62 to 0.75)	45 per 1,000	14 fewer per 1,000 (from 11 fewer to 17 fewer)
Stroke 90–94 mmHg	38,646 (1 study) 4 years	LOW[1] due to indirectness	RR 0.63 (0.56 to 0.71)	33 per 1,000	12 fewer per 1,000 (from 9 fewer to 14 fewer)
Stroke >95 mmHg	6,195 (1 study) 4 years	LOW[1] due to indirectness	RR 0.51 (0.41 to 0.63)	73 per 1,000	36 fewer per 1,000 (from 27 fewer to 43 fewer)

[1]Downgraded by 1 or 2 increments due to population or outcome indirectness
[2]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 7: Clinical evidence summary: Treatment versus no treatment at systolic blood pressure threshold of 140-159mmHg at low cardiovascular risk (without type 2 diabetes) – non-randomised evidence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects[3]	
				Risk with No treatment (no diabetes)	Risk difference with Treatment (95% CI)
Mortality 140–159 mmHg	38,286 (1 study)	VERY LOW[2] due to	HR 1.02 (0.88 to	41 per 1,000	1 more per 1,000 (from 5 fewer to 7 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects[3]	
				Risk with No treatment (no diabetes)	Risk difference with Treatment (95% CI)
	5.8 years	indirectness	1.18)[4]		
Stroke 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[1,2] due to, imprecision, indirectness	HR 0.97 (0.78 to 1.21)[4]	15 per 1,000	0 fewer per 1,000 (from 3 fewer to 3 more)
Myocardial Infarction 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[2] due to indirectness	HR 1.00 (0.80 to 1.25)[4]	15 per 1,000	0 fewer per 1,000 (from 3 fewer to 4 more)
Heart failure 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[1,2] due to imprecision, indirectness	HR 1.34 (0.96 to 1.87)[4]	7 per 1,000	2 more per 1,000 (from 0 fewer to 6 more)
Non-MI acute coronary syndrome 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[1,2] due to imprecision, indirectness	HR 1.19 (0.74 to 1.91)[4]	3 per 1,000	1 more per 1,000 (from 1 fewer to 3 more)
Hypotension 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[2] due to indirectness	HR 1.69 (1.30 to 2.20)[4]	8 per 1,000	6 more per 1,000 (from 3 more to 10 more)
Acute Kidney Injury 140–159 mmHg	38,286 (1 study) 5.8 years	VERY LOW[1,2] due to imprecision, indirectness	HR 1.37 (1 to 1.88)[4]	8 per 1,000	3 more per 1,000 (from 0 more to 7 more)

[1]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3]Absolute effects calculated by inputting raw event data from median follow up time into GRADE.
[4]Evidence based on one study that reported HRs with raw event data.

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

Four studies relating to this review question were identified but were excluded due to applicability or methodological limitations.[161,21,64,105] These are listed in appendix I, with reasons for exclusion given.

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

1.6.3 Health economic modelling

Methods

The clinical evidence review identified evidence in different blood pressure thresholds, but no evidence was identified relating to cardiovascular risk.

The committee agreed there was evidence to suggest relative treatment benefit in people with stage 1 hypertension (Systolic BP 140–159 mmHg), in terms of reducing cardiovascular events. But there was uncertainty about cost effectiveness in this population because the same relative treatment benefit would lead to different absolute benefits in people with lower cardiovascular risk compared to people with higher cardiovascular risk.

The current recommendations for treatment initiation amongst those with stage 1 hypertension incorporate a cardiovascular risk-based component, of 20%, in people without target organ damage, established cardiovascular disease, renal disease, or diabetes. This recommendation was based on consensus. The committee agreed that it was a high modelling priority for this guideline update to evaluate whether only initiating drug treatment in this population with a 10-year cardiovascular risk equivalent to 20% or greater was the most cost effective option.

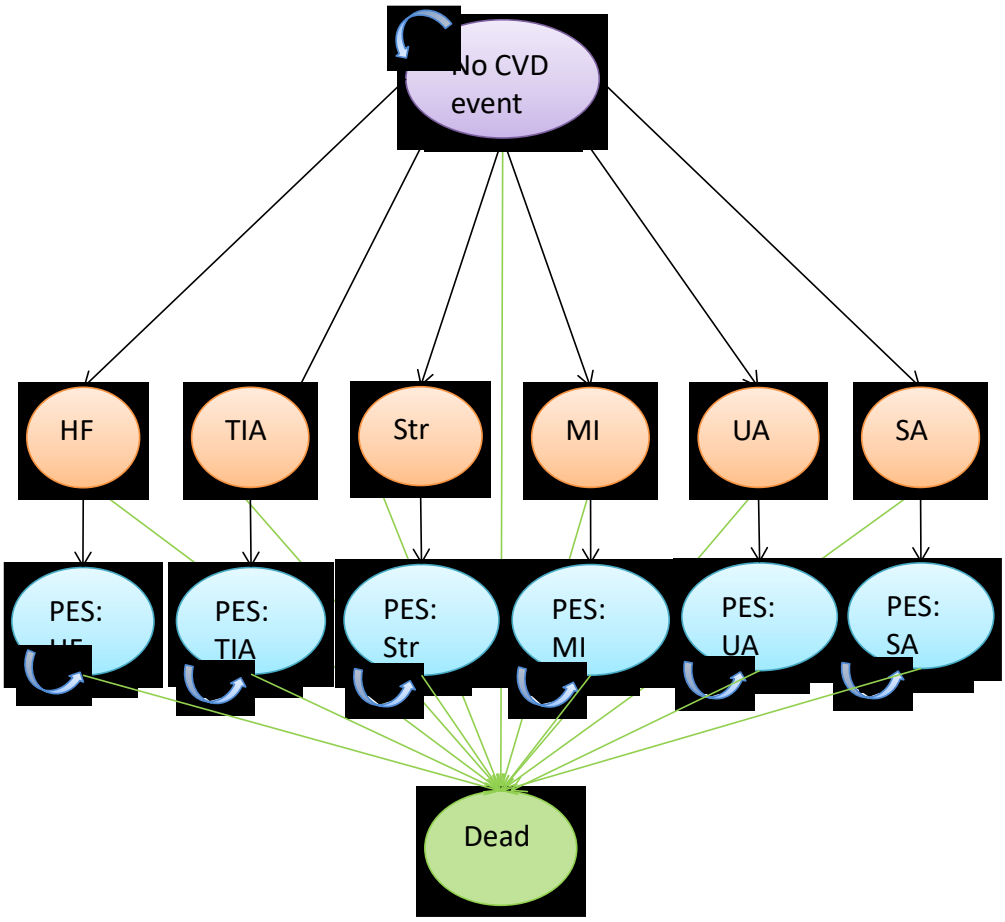
Therefore, the aim of the model was to investigate the cardiovascular risk level at which it is cost effective to initiate antihypertensive drug treatment in people with stage 1 hypertension without target organ damage, established cardiovascular disease, renal disease or diabetes.

A similar evaluation was recently undertaken as part of the NICE Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181)[133] guideline update, and it was agreed that it would be appropriate to take a similar approach for this guideline.

The model was a cost–utility analysis with a lifetime horizon comparing antihypertensive treatment with no antihypertensive treatment in a population with stage 1 hypertension with a base-case age of 60. The intervention and comparator were compared in 4 10-year QRISK cardiovascular risk subgroups to assess whether it is cost effective to use antihypertensive drug treatment in each risk group: 5%, 10%, 15% and 20%. Men and women were also compared separately. Additionally, other age groups were also evaluated: age 40, 50, 70 and 75.

The model structure was a Markov model with 1 year cycles. People begin in a ‘no cardiovascular event’ state and could transition to 6 non-fatal cardiovascular event health states of stable angina, unstable angina, myocardial infarction, transient ischaemic attack, stroke and heart failure, as well as 2 fatal states of cardiovascular and non-cardiovascular death. Each event state also had a respective post-event state where people move to in the following cycle after an event. Repeat events were not modelled.

Figure 1: Model structure



Abbreviations: CVD: cardiovascular disease; HF: heart failure; MI: myocardial infarction; PES: post-event state; SA: stable angina; Str: stroke; TIA: transient ischaemic attack; UA: unstable angina. The death state can include cardiovascular or non-cardiovascular death.

The cardiovascular risk subgroups were predefined, and the risk of a first event was determined by the distribution of this cardiovascular risk over the cardiovascular events in the model, which varies by age and sex. The distribution of events was taken from the NICE Lipids model. There was also an annual absolute increase in coronary heart disease risk that was applied to the coronary heart disease events of stable angina, unstable angina, and myocardial infarction. The same risk was applied to the other events depending on their frequency relative to the coronary heart disease events. This was assumed to capture that risk increases with age; therefore, that meant that beyond the 10-year period (as QRISK is a 10-year risk), cardiovascular risk would keep increasing linearly. This annual increase in coronary heart disease risk was higher for men than for women.

Treatment effect in the base case was taken from a meta-analysis (Brunström 2018)[41] included in the clinical review from the stage 1 hypertension population, as that was the population in the model. The same treatment effect was applied to all risk groups (which would lead to different absolute impact), but acknowledging that this was data from mostly intermediate/higher risk people. The risk of adverse events was taken from the targets clinical review for this guideline. The costs considered included; drug treatment and monitoring, adverse events (acute kidney injury [AKI] and falls), and treating cardiovascular events. For full details see appendix 1.

Results

The results of the model for the base-case age group (age 60) can be seen in Table 9.

Treatment was not cost effective at the 5% threshold. The probability of treatment being cost effective at 10% for men and women was around 84–86%.

Table 8: Base case results (per person, discounted)

	Undiscounted life-years	Total Costs	Total QALYs	ICER (£)	Prob Tx CE at £20k		Undiscounted life-years	Total Costs	Total QALYs	ICER (£)	Prob Tx CE at £20k
	Male						Female				
5% risk											
No Tx	23.66	£2,910	12.93		50%		26.16	£3,346	13.17		49%
Tx	23.78	£4,034	12.99	£20,524	50%		26.30	£4,465	13.23	£19,978	51%
10% risk											
No Tx	22.84	£4,169	12.52		15%		25.24	£5,241	12.73		12%
Tx	23.03	£5,105	12.61	£10,017	85%		25.46	£6,092	12.83	£8,635	88%
15% risk											
No Tx	22.09	£5,348	12.14		6%		24.41	£6,991	12.33		5%
Tx	22.34	£6,107	12.26	£5,969	94%		24.69	£7,602	12.46	£4,610	95%
20% risk											
No Tx	21.41	£6,443	11.78		3%		23.67	£8,621	11.96		3%
Tx	21.70	£7,062	11.93	£3,993	97%		23.99	£9,035	12.12	£2,566	97%

Note that values shaded red are above the NICE cost effectiveness threshold of £20,000 per QALY
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, No Tx = No treatment, QALYS = quality adjusted life-years, Tx = treatment.

Some work was undertaken to identify the minimum QRISK2 levels for someone aged 60 who is male or female in order to have some clinical context to interpret the risk thresholds predicted by the model (see Table 9, column labelled 1, for those aged 60). These minimum risk levels were found by using the QRISK2 online calculator – assuming a clinic systolic blood pressure of 140 mmHg, a low total to HDL cholesterol ratio of 2.5, and all other variables within the calculator were left blank. The minimum risk levels represent the healthiest version of someone of a particular age and sex with stage 1 hypertension.

As the minimum QRISK2 risk levels identified for men and women aged 60 with stage 1 hypertension (8.5% for men and 5.3% for women) were higher than the risk levels predicted by the model, above which treatment is cost effective, it would be cost effective to treat all people aged 60 with stage 1 hypertension. The probability of treatment being cost effective at the 5% level was around 50% for both sexes. However, as women tend to have a lower calculated risk, if a woman aged 60 was at very low risk (that is, close to the QRISK2 minimum risk level of 5.3%), then there is likely to be just as much uncertainty on whether treatment would be cost effective for that individual as whether no treatment would not be cost effective.

Results from the other age subgroups showed that the younger the population (those aged 40 and 50), the lower the risk level at which treatment becomes cost effective, as younger people have more time to benefit from treatment. Comparing the risk thresholds predicted from the model for each age group with the minimum risk levels calculated (see Table 9) showed that it was cost effective to treat all ages with stage 1 hypertension except women

aged 40 and 50, where the model risk thresholds were higher than the minimum risk levels, as risk is very low in younger women.

Table 9: Summary of risk thresholds for all age groups

Age	1) Minimum risk level from QRISK2	2) Risk threshold at which treatment becomes cost effective (from model)	Decision in clinical practice (a)
Male			
40	1.50%	0.66%	Treat all
50	4.00%	1.84%	Treat all
60	8.50%	5.02%	Treat all
70	16.40%	9.72%	Treat all
75	22%	11.43%	Treat all
Female			
40	0.90%	1.66%	Treat above 1.66% risk
50	2.30%	2.82%	Treat above 2.82% risk
60	5.30%	4.94%	Treat all
70	11.70%	7.53%	Treat all
75	17.00%	8.52%	Treat all

(a) Note: if the risk levels the model found were cost effective (column labelled 2) are lower than the minimum risk level (column labelled 1), then it is cost effective to treat everyone at that age, regardless of risk; otherwise, the model result is the lowest cost effective risk level.

It was acknowledged that the base-case analysis was a simplification of the reality in that those who are initially untreated are unlikely to remain untreated their entire lives, as the current recommendation lists various criteria that people with stage 1 hypertension can meet that would make them eligible for treatment, which they may develop in the future as well as potentially progressing to stage 2 hypertension. Because it was considered too complex to capture how these underlying risk factors would change over time in the model, a sensitivity analysis on differential treatment durations was undertaken. This involved testing arbitrary time points at which people in the no treatment arm started treatment, in order to mimic that people wouldn't stay untreated forever and to see how this would affect results. See Table 10 for results. For the base-case age group (age 60), the assumptions around differential treatment duration that were tested did not change the results because all risk thresholds identified were similar and were still lower than the minimum risk values from the QRISK2 calculator.

Testing differential treatment durations and whether that impacted the main conclusions for the other age groups, showed that in men it wasn't cost effective anymore to treat all men aged 40 and 50 if they were likely to develop other reasons for going onto treatment in shorter durations of time (1–10 years). For women, the conclusions did not change when differential treatment durations were tested.

Table 10: Differential treatment duration results for all ages

Years before meeting other criteria for treatment	Risk threshold				
	Age 40	**Age 50**	**Age 60**	**Age 70**	**Age 75**
MALES					
1	4.2%	4.1%	6.3%	10.6%	11.8%
5	3.5%	3.5%	5.6%	10.3%	11.6%
10	2.6%	2.7%	4.8%	-	-

20	1.3%	1.9%	-	-	-
Never (base case)	**0.7%**	**1.8%**	**5.0%**	**9.7%**	**11.4%**
Minimum risk level	***1.5%***	***4.0%***	***8.5%***	***16.4%***	***22.3%***
FEMALES					
1	2.6%	2.8%	4.8%	7.5%	8.1%
5	2.3%	2.6%	4.6%	7.6%	8.1%
10	2.0%	2.3%	4.5%	-	-
20	1.6%	2.6%	-	-	-
Never (base case)	**1.7%**	**2.8%**	**4.9%**	**7.5%**	**8.5%**
Minimum risk level	***0.9%***	***2.3%***	***5.3%***	***11.7%***	***17.0%***

The columns show the risk thresholds for the different age groups. The rows show the differential treatment durations tested, and also the results of the base case analysis for each age group (that is, where a lifetime of treatment was compared to a lifetime of no treatment). Additionally the minimum risk values from the QRISK2 are also presented with orange text. Cells that are orange show where it is cost effective to treat everyone at that age because the risk threshold the model predicted is lower than the minimum risk level.

Various sensitivity analyses were undertaken. Varying treatment effect to make it more or less favourable was undertaken probabilistically for all age groups. The model was very sensitive to more favourable treatment effect, and treatment became cost effective at the 5% risk level even for those aged 75. Other sensitivity analyses were only undertaken deterministically for the 60 year old group. Inputs that changed the results by making treatment cost effective even at 5% risk included smaller drug costs, higher health state costs, nurses undertaking monitoring, not including adverse events, having higher annual cardiovascular (CV) risk increases for women, and lower utilities. Various inputs that would bias against treatment (like increasing cost) made treatment less cost effective but hardly ever to the extent that the 10% risk subgroup was not cost effective.

Limitations of the model were that repeat events were not modelled, which made the model more conservative towards treatment. The model was also conservative in other ways such as there are some events the model hasn't captured that may be avoided by taking antihypertensive treatment. The model used the average long-term mortality ratios that may mean mortality immediately following an event has been underestimated. Some inputs have been taken from previous models and could be considered out of date, but these were checked with the committee who concluded it would be difficult to find more up-to-date data. Additionally, the assumption that people in the no treatment arm would remain on no treatment was a simplification, but this has been addressed through a sensitivity analysis. The variability in risk over time has not been captured due to limited data; thus, a more linear approach to increasing risk over time was taken. Adherence to treatment has also not been included, which would reduce the effectiveness of treatment on a population level if adherence is poor. However, overall, it is generally accepted that antihypertensive treatment is very cost effective. On balance, the model was felt to be conservative towards treatment.

1.6.4 Resource costs

Initiating drug treatment to different blood pressure or risk thresholds will involve drug and monitoring costs and may have varying cost offsets in terms of cardiovascular events avoided depending on the severity of the population. These trade-offs were explored in detail in the economic modelling.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 Treatment versus no treatment as systolic blood pressure thresholds (with and without type 2 diabetes)

Below 140 mmHg threshold

Low quality evidence from 1 study with 62,617–68,816 participants showed no clinically important difference between starting treatment at below 140 mmHg and not starting treatment for all-cause mortality or coronary heart disease at 4 years. Very low quality evidence from 1 study with 60,879 participants showed no clinically important difference for stroke or heart failure at 4 years.

140–159 mmHg threshold

Very low quality evidence from 1 study with 35,254–42,543 participants showed a clinically important benefit of starting treatment at 140–159 mmHg for all-cause mortality, stroke, coronary heart disease and heart failure at 4 years.

160 mmHg or above threshold

Low quality evidence from 1 study with 79,900 participants showed a clinically important benefit of starting treatment at 160 mmHg or above for all-cause mortality and stroke at 4 years. Very low quality evidence from 1 study with 78,617 participants showed a clinically important benefit of starting treatment at this threshold for reducing occurrence of coronary heart disease at 4 years. Low quality evidence from 1 study with 23,395 participants showed a clinically important benefit of starting treatment in terms of reducing occurrence of heart failure at 4 years.

1.7.1.2 Treatment versus no treatment as 140–159 mmHg systolic blood pressure thresholds (type 2 diabetes)

Moderate quality evidence from 1 study with 5,629-6,334 participants showed a clinically important benefit of starting treatment at 140–159 mmHg in terms of all-cause mortality, stroke and heart failure at 4.4 years.

1.7.1.3 Treatment versus no treatment as diastolic blood pressure thresholds (with and without type 2 diabetes)

Below 80 mmHg threshold

Very low quality evidence from 1 study with 42,599 participants showed a clinically important benefit of starting treatment at a diastolic blood pressure of below 80 mmHg in terms of stroke occurrence at 4 years.

80–84 mmHg threshold

Very low quality evidence from 1study with 37,516 participants showed a clinically important benefit of starting treatment at a diastolic blood pressure of 80–84 mmHg in terms of stroke occurrence at 4 years.

85–89 mmHg threshold

Low quality evidence from 1 study with 39,731 participants showed a clinically important benefit of starting treatment at a diastolic blood pressure of 85–89 mmHg in terms of stroke occurrence at 4 years.

90–94 mmHg threshold

Low quality evidence from 1 study with 38,646 participants showed a clinically important benefit of starting treatment at a diastolic blood pressure of 90–94 mmHg in terms of stroke occurrence at 4 years.

95 mmHg or above threshold

Low quality evidence from 1 study with 6,195 participants showed a clinically important benefit of starting treatment at a diastolic blood pressure of 95 mmHg or above in terms of stroke occurrence at 4 years.

1.7.1.4 Treatment versus no treatment at 140–159 mmHg systolic blood pressure thresholds (without type 2 diabetes, low cardiovascular risk)

Very low quality evidence from 1 study with 38,286 participants showed no clinically important difference for starting treatment at 140–159 mmHg compared to not starting treatment for stroke, myocardial infarction, heart failure,non-myocardial infarction acute syndrome and acute kidney injury at 5.8 years. Very low to low quality evidence from 1 study with 38,286 participants showed a clinically important harm of starting treatment at this threshold for mortality and hypotension at 5.8 years.

1.7.2 Health economic evidence statements

One original cost–utility analysis found that antihypertensive drug treatment was cost effective compared to no antihypertensive drug treatment for treating hypertension in people aged 60 with a 10% 10-year cardiovascular risk (ICER in men: £10,676 per QALY gained; ICER in women: £9,399 per QALY).

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered all-cause mortality, quality of life, stroke and myocardial infarction to be critical outcomes for decision-making. Heart failure, vascular procedures, angina and specific adverse events such as reduction in estimated glomerular filtration rate (eGFR) were also considered important for decision-making.

Most of the evidence identified covered outcomes of mortality, stroke and heart failure. No adverse event data were identified. Data on occurrence of coronary heart disease were used in the absence of evidence for myocardial infarction.

1.8.1.2 The quality of the evidence

The quality of the clinical effectiveness evidence was low to very low. Although risk of bias was generally low, serious indirectness and imprecision resulted in lower evidence quality and made the evidence base more difficult to interpret. Most of the RCTs included in this review included some participants who were beyond the scope of this guideline, such as

people with moderate to severe chronic kidney disease (CKD) and people with previous cardiovascular events. This was apparent at treatment initiated at clinic systolic blood pressure thresholds of less than 140 mmHg. The committee agreed that at this threshold, not many trials had been conducted to investigate the effectiveness of antihypertensive medication in those without diabetes, chronic kidney disease or previous cardiovascular events, and as a consequence, the evidence at this threshold was considered indirect. To ensure the evidence identified was applicable to the review question, studies that had an indirect population greater than 20% were excluded.

There was no evidence available for people with hypertension without type 2 diabetes; instead the evidence included was a mixed population. There was also no evidence available comparing treatment at different cardiovascular risk levels.

1.8.1.3 Committee discussion of the evidence

Mixed populations including people with and without type 2 diabetes

The committee discussed the evidence for initiating treatment at different systolic blood pressure thresholds in a mixed population, which included participants with primary hypertension and with or without type 2 diabetes. Data were not available for people without type 2 diabetes and hypertension alone as a distinct population, so the evidence was interpreted for both groups together. The committee noted that it was difficult to interpret evidence for treatment versus no treatment at a clinic blood pressure threshold below 140 mmHg. Because the committee was not aware of data based only on a primary prevention population in this group, it assumed that the data were likely to be based on people who had a previous cardiovascular event or chronic kidney disease. The data was therefore difficult to interpret to inform recommendations for primary prevention of cardiovascular events. The committee considered that people who had previously had a cardiovascular event would be at a higher risk of having further events; therefore, these people could benefit from treatment more, and these data could be overestimating the effect of treatment.

Regardless of this, there was no clinically important benefit for all-cause mortality when initiating treatment at less than 140 mmHg, and the committee agreed that there was no benefit of treating people at this level. The committee also discussed evidence for occurrence of stroke in people with a blood pressure of less than 140 mmHg, which demonstrated that there were 4 fewer strokes per 1,000 people in the treated group compared to the untreated group. The committee agreed this was not an adequate clinical benefit to justify treating all people with a systolic blood pressure of less than 140 mmHg. In addition, there was no clinically important benefit of treatment at this threshold for reducing coronary heart disease.

The committee found the data on occurrence of heart failure uninformative. Although there was a clinical benefit of treatment at all blood pressure thresholds, this was based just on the risk ratio without absolute event rates. As a result, the committee could not be as sure of the effect without the actual number of events that occurred. The committee also considered that the population included in the less than 140 mmHg group would have included people that had previous heart failure or coronary artery disease. This meant that the evidence in this group could be overestimating the efficacy of treatment. The committee could not determine the real importance of this treatment without the absolute event rates within each arm. The committee agreed there was no benefit of treating people with a systolic blood pressure less than 140 mmHg, particularly when the proportion of participants with established cardiovascular disease is taken into account.

The committee agreed that there was a clinically important benefit of treating people with a clinic blood pressure of 140–159 mmHg and greater than 160 mmHg. This was based on evidence for all-cause mortality, stroke and coronary heart disease. This was in a population believed to be of moderate cardiovascular risk given the average age and blood pressure of

the study population. It could be argued that any mortality avoided should be considered a benefit; however, what is also important in this review is the relation of the outcomes between different blood pressure groups. Because absolute event rates were not available for all outcomes, the committee found that looking at the relative risks of the different groups simultaneously to infer a pattern was useful, in order to identify if there was a threshold at which there is no (or less of a) treatment benefit. When considering the all-cause mortality evidence in this way, the committee agreed that there was a benefit of treating people with a systolic blood pressure above 140 mmHg. For the data on stroke and coronary heart disease, the committee agreed that the evidence demonstrated benefit in treating groups with a blood pressure of 140–159 mmHg and greater than 160 mmHg. An observational study found treating people with stage 1 hypertension who were labelled as low risk (based on inclusion criteria not formal assessment) did not provide any benefit in terms of reduction in cardiovascular events but did lead to harms. The committee acknowledged that this was lower quality evidence, but agreed that it did highlight there is uncertainty around the effectiveness (and hence cost effectiveness) of treatment in lower risk groups amongst those with stage 1 hypertension (whereas the previous guideline recommendation focused on treating those at higher risk of cardiovascular events). The committee agreed that this evidence did not answer this question fully, as there was no clinical evidence identified in specific risk groups.

Taking the body of evidence into account, the committee was not convinced that a change in guidance to treat below stage 1 hypertension was warranted. The committee kept in mind that any change in these recommendations would need to be based on high quality evidence, and it was not convinced that the systematic reviews included in this review answered the review question fully, or that the outcomes were high enough quality, to warrant any change in practice. Regardless of this, the evidence did not contradict current recommendations. However, it did raise the question of whether all people with stage 1 hypertension should be treated.

For the evidence informing the outcomes for treating at different diastolic blood pressure thresholds, the committee agreed that as there was no clear gradation of risk in the control groups (for example, the control group event rate was lower in the 90–94 mmHg group than it was in the 85–89 mmHg group). This did not lead to confidence in the results, as it is expected that risk would increase as diastolic blood pressure increases. The committee agreed it was difficult to make a decision based on diastolic blood pressure alone, as people with low diastolic blood pressure tend to have the highest systolic blood pressure. It was unclear what the systolic blood pressure level was within each group, and as a result, the data were difficult to interpret. The committee therefore agreed that this evidence would not change the current recommendations on diastolic blood pressure thresholds.

People without type 2 diabetes

The evidence showed a harm of treatment for mortality at a clinical systolic blood pressure of 140-159mmHg, because any difference in mortality was considered clinically important. The evidence also showed clinically important harm of treatment in relation to hypotension, with 6 more hypotension events per 1000 and a HR of 1.69. There was no difference in stroke, MI events, heart failure, acute coronary syndromes or acute kidney injury. The committee found it difficult to interpret this evidence, due to the considerable uncertainty around each effect estimate. The evidence therefore showed that the benefit of treating people with stage 1 hypertension at lower blood pressure and risk thresholds was uncertain. The mean cardiovascular risk score (QRISK2) within the population was approximately 8%, although the methods for calculating actual risk involved some imputation and therefore was limited in its ability to accurately define the population at a particular risk threshold. Furthermore, 41.6% of participants in the non-treatment arm were on antihypertensive treatment at some point in the trial, which could have influenced the effect sizes. Taking all of this into account, the committee agreed that the evidence for treatng people at lower risk with type 2 diabetes and stage 1 hypertension was limited.

People with type 2 diabetes

The committee discussed the evidence for antihypertensive treatment for people with type 2 diabetes and stage 1 hypertension. The evidence for people with type 2 diabetes was very low quality due to indirectness and imprecision, and because the evidence was based on one cohort study. It agreed there was a clear benefit of treatment at a clinic blood pressure of greater than 160/100mmHg for all-cause mortality, stroke and heart failure as patients with type 2 diabetes would be at higher risk than thos with hypertension alone. The evidence for the 140-159mmHg studies showed that the clearest signal of benefit was for all-cause mortality and stroke, with 22 fewer deaths and 19 fewer strokes per 1000 respectively.

Although no evidence was identified for the treatment of people with a clinic systolic blood pressure of less than 140 mmHg, the committee was aware of a number of RCTs and systematic reviews that reported no benefit of treating this group, even though they included trials that recruited people at higher risk of events than those covered in this guideline, for example by requiring the presence of target organ damage such as albuminuria or additional cardiovascular risk factors; so it would be expected for the treatment benefit to be higher. The committee therefore agreed that there was no evidence to suggest a different threshold for people with hypertension and diabetes than without diabetes. This is a small change from the diabetes guideline; the previous recommendations for people with type 2 diabetes (NG28) suggested initiation of antihypertensive medication if lifestyle interventions alone did not reduce blood pressure to below 140/80 mmHg or 130/80 mmHg in the presence of kidney, cerebrovascular or eye disease. Evidence for lower treatment initiation thresholds in people with type 2 diabetes was limited within this review, with evidence available for treatment initiation above 140/90mmHg only and limited to patients with hypertension. The committee was aware of some evidence to suggest that lower blood pressure thresholds did not reduce the rate of cardiovascular events. The previous recommendations for people with type 2 diabetes (NG28) were based on 2 small studies in people without hypertension. Furthermore, these 2 studies were not designed to measure the benefit of treatment in people who already had target organ damage but rather the studies predominantly assessed the incidence of target organ damage based on a target diastolic blood pressure. The committee therefore felt that there was insufficient evidence to recommend a different blood pressure treatment threshold for this subgroup. Discussion of the appropriate blood pressure target for patients with diabetes and significant albuminuria or other target organ damage was outside the scope of this guideline.

1.8.2 Cost effectiveness and resource use

No published economic evidence was identified for this question.

The clinical review identified some evidence comparing treatment versus no treatment in groups with different levels of systolic blood pressure. This showed that treatment was generally clinically effective at reducing cardiovascular events in a mixed primary prevention population with stage 2 hypertension. The committee also concluded that there was insufficient clinical evidence to support initiation of drug treatment below the current definition of stage 1 hypertension and noted that there is a lack of primary prevention studies in people with blood pressure <140 mmHg and the evidence found in this group was likely to contain some secondary prevention populations.

For those with stage 1 hypertension, the RCT evidence from the review showed that there was some clinical benefit to treating this population, although the committee noted that this is likely to be in intermediate or higher risk individuals based on the average characteristics and the lack of published RCT data on low risk individuals. An observational study that was included in this stage 1 population, specifically in lower risk individuals, suggested that treatment has limited benefit but does have harms. As these studies are in different CV risk populations, it confirmed to the committee that there is uncertainty around treatment effect in different risk groups. The 2011 recommendations for treatment initiation in those with stage 1

hypertension incorporate a cardiovascular risk-based component (of 20%), which was based on consensus. Given this, and also that the clinical evidence showed some benefit to treatment in the stage 1 group (but this was likely to be in people with intermediate or higher risk), the committee agreed that it was a high modelling priority for this guideline update to evaluate at what cardiovascular risk level antihypertensive drug treatment is cost effective in people without target organ damage, established cardiovascular disease, renal disease or diabetes.

The model was a cost–utility analysis with a lifetime horizon, comparing antihypertensive treatment with no antihypertensive treatment in a population with stage 1 hypertension with a base-case age of 60. The intervention and comparator were compared in 4 QRISK 10-year cardiovascular risk subgroups to assess whether it is cost effective to use antihypertensive drug treatment in each risk group: 5%, 10%, 15% and 20%. Men and women were also compared separately. Additionally, other age groups were also evaluated: ages 40, 50, 70 and 75. A Markov model was used where people begin in a 'no cardiovascular event' state, and can transition to 6 non-fatal cardiovascular event health states of stable angina, unstable angina, myocardial infarction, transient ischaemic attack, stroke and heart failure, as well as 2 fatal states of cardiovascular and non-cardiovascular death. Repeat events were not modelled. The costs considered included drug treatment and monitoring, adverse events (acute kidney injury [AKI] and falls), and treating cardiovascular events. The model methods are summarised in section 1.6.3, with full methods reported in Appendix 1.

The results of the model showed that in the base-case age group (age 60), treatment was cost effective at a 10 year cardiovascular risk threshold of just over 5% for both men and women (5.4% for men and 5.3% for women). The probability of treatment being cost effective at 10% for men and women aged 60 was around 85-88%. Comparison of these thresholds with the minimum QRISK2 levels for men and women aged 60 showed that it would be cost effective to treat all people aged 60 with stage 1 hypertension. The probability of treatment being cost effective at the 5% level was around 50% for both sexes, but uncertainty is likely to be higher in women, as they tend to have lower calculated risk: if a woman aged 60 was at very low risk (that is, close to the QRISK2 minimum risk level of 5.3%), then there would be significant uncertainty as to whether treatment or no treatment was the most cost effective option.

Results from the other age subgroups showed that in those aged 40 and 50, the lower the risk level that it was cost effective to treat above, as younger people live longer and thus have more time to benefit from treatment. In the age 70 and 75 subgroups, treatment was cost effective either in the 10% or 15% risk groups (depending on age and gender). Comparing the risk thresholds the model predicted for each age group with the minimum risk levels calculated showed that it was cost effective to treat all ages with stage 1 hypertension except women aged 40 and 50, where the model risk thresholds were higher than the minimum risk levels: risk is very low in younger women.

A sensitivity analysis on differential treatment durations was undertaken to take into account that people may become eligible for treatment in the future for other reasons. This involved testing arbitrary time points at which people in the no treatment arm started treatment, in order to imitate subsequent treatment and to see how this would affect results. For the base-case age group (60), the assumptions around differential treatment duration that were tested did not change the results because all risk thresholds identified were similar and were still lower than the minimum QRISK2 values. Testing differential treatment durations and whether that impacted the main conclusions for the other age groups, showed that in men it wasn't cost effective anymore to treat all men aged 40 and 50 if they were likely to develop other reasons for going onto treatment in shorter durations of time 1–10 years. For women, the conclusions did not change when differential treatment durations were tested.

The model was very sensitive to a more favourable treatment effect, as treatment became cost effective at the 5% risk level even for those aged 75. Conversely, no treatment benefit

would mean antihypertensive treatment is not cost effective. Other sensitivity analyses were only undertaken deterministically for the 60-year-old group. Inputs that changed the results by making treatment cost effective even at 5% risk included smaller drug costs, higher health state costs, nurses undertaking monitoring, not including adverse events, events, having higher annual cardiovascular (CV) risk increases for women, and lower utilities. Various inputs that would bias against treatment (like increasing cost) made treatment less cost effective but hardly ever to the extent that the 10% risk subgroup was not cost effective.

The committee's interpretation of the economic model was that it was overall conservative towards treatment, but they had greater confidence that treating at 10% risk was cost effective compared to 5% risk in the base-case age group results. There was also more uncertainty around people younger than 60 because it was shown not to be cost effective to treat all women aged 40 and 50 with stage 1 hypertension, and the conclusions changed for men aged 40 and 50 in the differential treatment durations. Treating at a younger age also subjects people to more years of treatment, and there were also concerns about over-medicalisation of younger people at low risk of subsequent cardiovascular events. Conversely, there were concerns that lifetime risk in a young hypertensive would be relatively high and that delaying treatment might lead to preventable harm. Additionally, stage 1 hypertension in a younger age group, for example age 40, is more likely to lead to early onset target organ damage, so a greater proportion will subsequently be eligible for treatment. The observational study included in the guideline review, by Sheppard et al, suggested that low-risk individuals (with an average risk of 8%) are unlikely to benefit from treatment. The committee opinion was that this supported the conclusions of the model in terms of there being a higher level of confidence in a more conservative threshold of 10%, because there is uncertainty about treatment effect in lower risk people. Additionally, a recent sub-study of the SPRINT trial looking at the effect of intensive versus standard treatment in cardiovascular risk subgroups showed that in those with lower risk there was more harm than benefit from treatment, whereas those with higher risks had higher benefits, supporting that there is a higher absolute benefit from treatment to those at higher risk.

Clinicians often find it more helpful to explain the benefits of treatment to people in terms of numbers needed to treat (NNT). The 10-year minimum risk levels calculated from the QRISK2 were converted to 5-year risks (as 5-year NNTs are more typical) and combined with the relative treatment effect used in the model to derive NNTs. The committee agreed that these confirmed their previous thinking that the NNTs for antihypertensive treatment in a stage 1 population were favourable.

The committee discussed what it would currently do in practice and noted there is variation in how the recommendation from CG127 of treating above a 20% cardiovascular risk threshold has been implemented. Some UK research by Sheppard et al[156] using CPRD data on people with untreated stage 1 hypertension and average age of 52 years showed that around half were already receiving either antihypertensive treatment alone or antihypertensive treatment alongside lifestyle advice. Given the average age of the population in this study, it was likely that the cardiovascular risk for that population was significantly below the current 20% CVD risk threshold forinitiation of drug therapy and likely in the range of 5–15%. Some clinicians who see younger people who might have a low 10 year risk but have sustained stage 1 hypertension would offer treatment to those individuals even in the absence of established target organ damage as their lifetime risk is significant. Some risk factors such as family history of hypertension are not included in the QRISK CVD calculator but have a significant disease-associated effect for hypertension and would disproportionately manifest in younger age groups. Furthermore, some clinicians appear to be of the opinion that the threshold to treat hypertension is 10% because that is the threshold recommended in the Lipids guideline for treatment of risk of atherosclerotic disease as the process of atherosclerosis involves both risk factors and they do not differentiate their importance based on therapy effects. Overall, there is significant heterogeneity as to whether an individual is offered treatment (and whether it is implemented). The committee acknowledged the difficulty in its discussion

of being able to suggest a single rule about who should and should not be treated and how this would be done on an individualised basis in clinical practice.

The committee agreed advice on lifestyle modifications should be offered to all with hypertension and in particular to be the first intervention offered when someone is identified as having stage 1 hypertension. Sheppard et al identified that not everyone that is on treatment has had prior lifestyle advice recorded.

Overall, the committee discussed the many different factors that would need to be considered in order to reach a recommendation: (1) the results of the model and the confidence in treatment benefit in different risk levels; (2) the variability in how the current risk threshold recommended is applied; (3) individual patient choice; and (4) the resource impact and population that will potentially be affected by lowering the risk threshold.

The committee agreed that an acceptable compromise was to discuss starting treatment above a risk level of 10%, and to consider treatment below a risk level of 10% in specific populations. A 10% risk threshold would also be in line with the threshold from CG181; therefore, this would translate into practice more easily if treatment for different cardiovascular disease risk factors had a common threshold. The committee noted how the current age that people are generally started on antihypertensive treatment was around age 60 and had evidence from UK practice that many people are started on antihypertensive treatment at a lower age. This is in keeping with a risk threshold of 10% already being the established default in clinical practice because using the minimum risk values that were used for validation in the model: a man or woman would have 10% risk at between the age of 60 and 70. The recommendation on considering treatment in those below 10% defined this population as adults aged under 60. This recommendation was intending to target younger individuals with low risk in whom, as discussed above, there is less certainty about treatment benefit, but lifetime risk may also be underestimated from 10 year risk calculators. Additionally, individual preferences and circumstances are likely to have the biggest impact on the treatment decision in yonger people. Age 60 was chosen because this is around the age at which an individual would become 10% risk as mentioned, and also because of the concern that below this age there are larger discrepancies between the 10 year and lifetime risk.[92] In addition, due to age alone someone over 60 is unlikely to have a risk under 10%.

A ‘consider’ recommendation was also made for people aged over 80 whose blood pressure is over 150/90, who previously did not have a specific recommendation and therefore this was interpreted in practice as they should not be treated. The committee felt there were many factors to consider with regards to starting treatment above the age of 80 such as co-morbidities and again an individualised discussion should be had.

These recommendations are likely to have a significant cost impact due to the number of people affected and the predictable increase in monitoring visits and drug treatment that will be involved. Although this will somewhat be offset by the cardiovascular events avoided from more people being on treatment. The exact extent of the cost impact is uncertain depending on how closely the current threshold for treatment is being followed in practice. Treating at a lower threshold might also have other benefits aside from reducing cardiovascular events, such as the earlier detection of severe forms of hypertension, as people who are not on drug treatment are less likely to return for regular monitoring.

1.8.3 Other factors the committee took into account

The committee noted that family origin is one of the factors taken into account in cardiovascular risk assessments such as QRISK, which increases the estimated CV risk within this population. Therefore, all people irrespective of family origin are adequately addressed by these recommendations.

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Appendices

Appendix A: Review protocols

Table 11: Review protocol: Initiating treatment

Field	Content
Review question	At what blood pressure and/or cardiovascular disease risk threshold should antihypertensive drug treatment be initiated for adults with hypertension?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To establish which blood pressure or cardiovascular disease risk threshold antihypertensive drug treatment should be initiated at.
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) who are not on current pharmacological treatment for hypertension (minimum wash-out 4 weeks) Stratify by: • Presence or absence of type 2 diabetes • Cardiovascular or blood pressure baseline risk

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Treatment initiation at different thresholds
	
	• Systolic blood pressure targets:
	  ○ Below120
	  ○ 120–129
	  ○ 130–139 mmHg
	  ○ 140–59 mmHg
	  ○ 160 mmHg or above
	• Diastolic blood pressure targets:
	  ○ <80 mmHg
	  ○ 80–84 mmHg
	  ○ 85–89 mmHg
	  ○ 90–94 mmHg
	  ○ 95 mmHg or above
	
	Cardiovascular risk thresholds:
	1. 5–9%
	2. 10–14%
	3. 15–19%
	4. Above 20%
	
	Data will be preferentially extracted if they compare across or within these categories; however, other comparisons will be considered in the absence of this.

Eligibility criteria – comparator(s) / control or reference (gold) standard	Compared against each other (comparing different blood pressure and/or cardiovascular risk thresholds) Also within each other
Outcomes and prioritisation	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.

	Critical • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction **Important** • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Treatment related admission • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]
Eligibility criteria – study design	1. SRs (including IPD analyses) and RCTs that stratify or subgroup by baseline cardiovascular risk or blood pressure 2. Non-randomised studies that stratify by baseline cardiovascular risk or blood pressure • Confounders that should be adjusted for: o age o prior CV event o smoking o sex o BP (CV risk) Note: • Treatment must be received for a minimum of 1 year in study • Where an IPD meta-analysis is available that matches the protocol, this will be included and data published since will be presented separately. IPD meta-analysis is considered the highest quality evidence, therefore lower quality evidence will only be considered if it was published after the IPD.
Other inclusion exclusion criteria	Exclusions: • Non-comparative data where all participants start at the same treatment threshold (studies that do not stratify by 2 or more blood pressure or CV risk groups) • Studies including participants with type 1 diabetes or chronic kidney disease (A3 [heavy proteinuria]) or A2 or above for participants with type 2 diabetes. • Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn's adenoma, phaeochromocytoma, renovascular hypertension). • Pregnant women. • Children (under 18 years).
Proposed sensitivity / subgroup analysis, or meta-regression	No subgroups identified. The committee agreed that the stratification and adjustments required by this protocol encompassed the relevant confounding factors.
Selection process – duplicate screening / selection / analysis	Duplicate screening, selection and analysis will be undertaken on this review. A senior research fellow will undertake quality assurance prior to

	completion.
Data management (software)	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Medline, Embase, the Cochrane Library Date cut off: 2000 (restrict to papers published after this date) Language: Restrict to English only Key papers: Cochrane review (2017): http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010316.pub2/full
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for 1 database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details, please see section 6.2 of Developing NICE guidelines: the manual 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/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Anthony Wierzbicki in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.

Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 12: 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. No date cut-off from the previous guideline was used.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. 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).[134] **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 exclude selectively the remaining studies. All studies excluded based on 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 US 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 2002 or later (including any such studies included in the previous guideline[s]) but that depend on unit costs and resource data entirely or predominantly before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline[s]) 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. • Generally, economic evaluations based on excludes from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used

Database	Dates searched	Search filter used
Medline (OVID)	1946–02 October 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974–02 October 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 8 of 12, August 2018 CENTRAL to Issue 7 of 12, July 2018 DARE and NHS EED to Issue 2 of 4, April 2015 HTA to Issue 4 of 4, October 2016	None

Table 14: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Hypertension, Pregnancy-Induced/ not exp Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/ not exp Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/8-15
17.	7 not 16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/

31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	limit 38 to English language
40.	exp antihypertensive agents/
41.	(anti-hypertens* or antihypertens* or anti hypertens*).ti,ab.
42.	40 or 41
43.	risk factors/
44.	risk assessment/
45.	((initiat* or start* or commenc* or begin*) adj4 (treatment* or medicat*)).ti,ab.
46.	(risk* adj2 (factor* or assess*)).ti,ab.
47.	(threshold* or level*).ti,ab.
48.	or/43-47
49.	39 and 42 and 48
50.	randomized controlled trial.pt.
51.	controlled clinical trial.pt.
52.	randomi#ed.ti,ab.
53.	placebo.ab.
54.	randomly.ti,ab.
55.	Clinical Trials as topic.sh.
56.	trial.ti.
57.	or/50-56
58.	Meta-Analysis/
59.	exp Meta-Analysis as Topic/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(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.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	Epidemiologic studies/
70.	Observational study/
71.	exp Cohort studies/
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

74.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	Controlled Before-After Studies/
76.	Historically Controlled Study/
77.	Interrupted Time Series Analysis/
78.	(before adj2 after adj2 (study or studies or data)).ti,ab.
79.	or/69-78
80.	exp case control study/
81.	case control*.ti,ab.
82.	or/80-81
83.	79 or 82
84.	Cross-sectional studies/
85.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	or/84-85
87.	79 or 86
88.	79 or 82 or 86
89.	49 and (57 or 68 or 88)

Table 15: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Maternal Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/8-15
17.	7 not 16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/

29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	34 not 35
37.	limit 36 to English language
38.	exp antihypertensive agent/
39.	(anti-hypertens* or antihypertens* or anti hypertens*).ti,ab.
40.	38 or 39
41.	risk factor/
42.	risk assessment/
43.	((initiat* or start* or commenc* or begin*) adj4 (treatment* or medicat*)).ti,ab.
44.	(risk* adj2 (factor* or assess*)).ti,ab.
45.	(threshold* or level*).ti,ab.
46.	or/41-45
47.	37 and 40 and 46
48.	random*.ti,ab.
49.	factorial*.ti,ab.
50.	(crossover* or cross over*).ti,ab.
51.	((doubl* or singl*) adj blind*).ti,ab.
52.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
53.	crossover procedure/
54.	single blind procedure/
55.	randomized controlled trial/
56.	double blind procedure/
57.	or/48-56
58.	systematic review/
59.	meta-analysis/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(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.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	Clinical study/
70.	Observational study/
71.	family study/
72.	longitudinal study/
73.	retrospective study/

74.	prospective study/
75.	cohort analysis/
76.	follow-up/
77.	cohort*.ti,ab.
78.	76 and 77
79.	(cohort adj (study or studies or analys* or data)).ti,ab.
80.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
81.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	(before adj2 after adj2 (study or studies or data)).ti,ab.
83.	or/69-75,78-82
84.	exp case control study/
85.	case control*.ti,ab.
86.	or/84-85
87.	83 or 86
88.	cross-sectional study/
89.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
90.	or/88-89
91.	83 or 90
92.	83 or 86 or 90
93.	47 and (57 or 68 or 92)

Table 16: Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hypertension] explode all trees
#2.	hypertens*:ti,ab
#3.	(elevat* near/2 blood next pressur*):ti,ab
#4.	(high near/1 blood near/1 pressur*):ti,ab
#5.	(increase* near/2 blood pressur*):ti,ab
#6.	((systolic or diastolic or arterial) near/2 pressur*):ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Antihypertensive Agents] explode all trees
#9.	(anti-hypertens* or antihypertens* or anti hypertens*):ti,ab
#10.	#8 or #9
#11.	MeSH descriptor: [Risk Factors] explode all trees
#12.	MeSH descriptor: [Risk Assessment] explode all trees
#13.	((initiat* or start* or commenc* or begin*) near/4 (treatment* or medicat*)):ti,ab
#14.	(risk* near/2 (factor* or assess*)):ti,ab
#15.	(threshold* or level*):ti,ab
#16.	#11 or #12 or #13 or #14 or #15
#17.	#7 and #10 and #16

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to hypertension in adults population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for

Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014–28 August 2018	Exclusions Health economics studies
Embase	2014–28 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception–28 August 2018 NHSEED - Inception to March 2015	None

Table 18: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Economics/
29.	Value of life/
30.	exp "Costs and Cost Analysis"/
31.	exp Economics, Hospital/
32.	exp Economics, Medical/

33.	Economics, Nursing/
34.	Economics, Pharmaceutical/
35.	exp "Fees and Charges"/
36.	exp Budgets/
37.	budget*.ti,ab.
38.	cost*.ti.
39.	(economic* or pharmaco?economic*).ti.
40.	(price* or pricing*).ti,ab.
41.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
42.	(financ* or fee or fees).ti,ab.
43.	(value adj2 (money or monetary)).ti,ab.
44.	or/28-43
45.	27 and 44

Table 19: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/

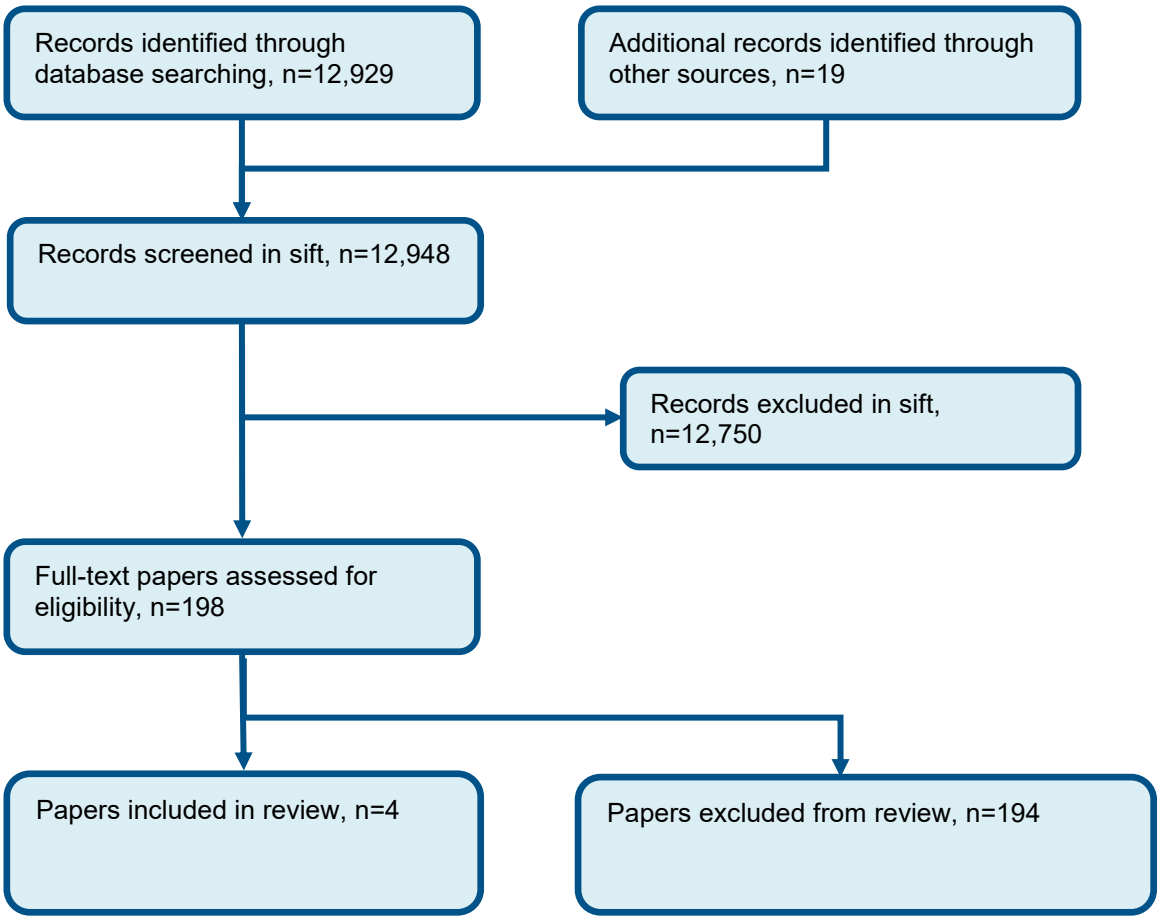
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

Table 20: NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED,HTA
#2.	(Hypertens*) IN NHSEED, HTA
#3.	(elevat* adj2 blood adj pressur*) IN NHSEED, HTA
#4.	(high adj blood adj pressur*) IN NHSEED, HTA
#5.	(increase* adj2 blood pressur*) IN NHSEED, HTA
#6.	((systolic or diastolic or arterial) adj2 pressur*) IN NHSEED, HTA
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix C: Clinical evidence selection

Figure 2: Flow chart of clinical study selection for the review of initiating treatment in Hypertension



Appendix D: Clinical evidence tables

Study	Brunström 2018[41]
Study type	Systematic Review
Number of studies (number of participants)	51 (n=192,795)
Countries and setting	Conducted in Multiple countries
Line of therapy	First line
Duration of study	Other: Each trial included had a minimum of 1,000 patient-years follow-up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed diabetic population
Subgroup analysis within study	Not applicable
Inclusion criteria	Randomized clinical trials with at least 1,000 patient-years of follow-up, comparing BP-lowering drugs versus placebo or different BP goals were included
Exclusion criteria	People with heart failure or left ventricular dysfunction and trials in the acute phase after myocardial infarction
Age, sex and family origin	Age - Other: Mean age 63.6 years. Sex (M/F): 60.1%/39.9%. Family origin: Multiple
Indirectness of population	Very serious indirectness: 23% of the population included with CAD, post-stroke, mixed CVD.
Interventions	Intervention 1: Blood pressure threshold – 130–139 mmHg. People with blood pressure of <140 mmHg treated with antihypertensives. Duration over 1,000 person-years. Concurrent medication/care: Not stated. Indirectness: Serious indirectness; Indirectness comment: included trials with indirect population Intervention 2: Blood pressure threshold - 140–159 mmHg. People with blood pressure 140–159 mmHg treated with anti-hypertensives. Duration over 1,000 person-years. Concurrent medication or care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Included trials with indirect population Intervention 3: Blood pressure threshold - greater than or equal to 160 mmHg. People with blood pressure greater or equal to 160 mmHg treated with antihypertensives. Duration over 1,000 person-years. Concurrent medication or care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Included trials with indirect populations

	Intervention 4: Blood pressure threshold - 130–139 mmHg. People with blood pressure of <140 mmHg not treated with antihypertensives. Duration over 1,000 person-years. Concurrent medication or care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Included trials with indirect populations Intervention 5: Blood pressure threshold - 140–159 mmHg. People with blood pressure 140–159 mmHg untreated. Duration over 1,000 person-years. Concurrent medication/care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Included trials with indirect populations Intervention 6: Blood pressure threshold – greater than or equal to 160 mmHg. People with blood pressure equal to or greater than 160 mmHg untreated. Duration 1,000 person-years. Concurrent medication/care: Not stated. Indirectness: Serious indirectness; Indirectness comment: Included trials with indirect population Note: total number of participants in each intervention unclear
Funding	Other (Of the 74 trials included, 70 reported funding. 56 were funded by industry and 14 by government grants or academia.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: <140 mmHg TREATED versus <140 mmHg CONTROL

Protocol outcome 1: All-cause mortality
- Actual outcome for Mixed diabetic population: All-cause mortality at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Stroke (ischaemic or haemorrhagic)
- Actual outcome for Mixed diabetic population: Stroke at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 3: Heart failure needing hospitalisation
- Actual outcome for Mixed diabetic population: Heart failure at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness;

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 140–159 mmHg TREATED versus 140–159 mmHg CONTROL

Protocol outcome 1: All-cause mortality
- Actual outcome for Mixed diabetic population: All-cause mortality at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Stroke (ischaemic or haemorrhagic) - Actual outcome for Mixed diabetic population: Stroke at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness Protocol outcome 3: Heart failure needing hospitalisation - Actual outcome for Mixed diabetic population: Heart failure at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GREATER THAN OR EQUAL TO 160 mmHg TREATED versus GREATER THAN OR EQUAL TO 160 mmHg CONTROL Protocol outcome 1: All-cause mortality - Actual outcome for Mixed diabetic population: All-cause mortality at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: Stroke (ischaemic or haemorrhagic) - Actual outcome for Mixed diabetic population: Stroke at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness Protocol outcome 3: Heart failure needing hospitalisation - Actual outcome for Mixed diabetic population: Heart failure at >1,000 person-years; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life; Myocardial infarction; Vascular procedures (including lower limb, coronary and carotid artery procedures); Angina needing hospitalisation; Acute kidney injury; New onset diabetes; Treatment related admission; Hypotension (dizziness)

Study	Law 2009[107]
Study type	Systematic Review
Number of studies (number of participants)	147 (n=464,000)
Countries and setting	Conducted in Multiple countries
Line of therapy	First line
Duration of study	Other: at least 1 year follow-up
Method of assessment of guideline condition	Systematic review: method of assessment mixed
Stratum	Mixed diabetic population
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Participants with no history of vascular disease, a history of coronary heart disease or a history of stroke
Exclusion criteria	Non-randomised trials and trials in which treated groups but not control groups had other interventions as well as blood pressure reduction, such as cholesterol reduction. Trials in people with chronic renal failure because these people typically have high blood pressure and high rates of cardiovascular disease and their response to standard blood pressure lowering therapy may differ from other people. Trials in which fewer than 5 coronary heart disease events and strokes were recorded or the duration of treatment was less than 6 months.
Age, sex and family origin	Age - Other: mean 64 years. Sex (M:F): Not stated. Family origin: Mixed
Extra comments	46,4000 adults with a total of 22,115 coronary heart disease events, 12,034 stroke events, 17,890 heart failure events, systolic blood pressure range of 112–194 mmHg, diastolic blood pressure range of 70–119.
Indirectness of population	Very serious indirectness: Indirect populations included with comorbidities such as CAD, stroke, heart failure
Interventions	(n=21,807) Intervention 1: Diastolic blood pressure threshold - <80 mmHg. Treated people. Duration 4 years. Concurrent medication or care: Indirect population taking other drugs. Indirectness: Very serious indirectness (n=18,780) Intervention 2: Diastolic blood pressure threshold – 80–84 mmHg treated people. Duration 4 years. Concurrent medication or care: Indirect population taking other drugs. Indirectness: Very serious indirectness (n=23,105) Intervention 3: Diastolic blood pressure threshold – 85–89 mmHg treated people. Duration 4 years. Concurrent medication or care: Indirect population taking other drugs. Indirectness: Very serious indirectness (n=19,368) Intervention 4: Diastolic blood pressure threshold – 90–94 mmHg treated people. Duration 4

	years. Concurrent medication or care: Indirect population taking other drugs. Indirectness: Very serious indirectness (n=3,331) Intervention 5: Diastolic blood pressure threshold – greater than or equal to 95 mmHg treated people. Duration 4 years. Concurrent medication or care: Indirect population taking other drugs. Indirectness: Very serious indirectness (n=20,792) Intervention 6: Diastolic blood pressure threshold – <80 mmHg untreated people. Duration 4 years. Concurrent medication or care: taking other drugs. Indirectness: Very serious indirectness (n=18,736) Intervention 7: Diastolic blood pressure threshold – 80–84 mmHg untreated people. Duration 4 years. Concurrent medication or care: taking other drugs. Indirectness: Very serious indirectness (n=16,626) Intervention 8: Diastolic blood pressure threshold – 85–89 mmHg untreated people. Duration 4 years. Concurrent medication or care: taking other drugs. Indirectness: Very serious indirectness (n=19,278) Intervention 9: Diastolic blood pressure threshold - 90-94 mmHg untreated people. Duration 4 years. Concurrent medication or care: taking other drugs. Indirectness: Very serious indirectness (n=2,864) Intervention 10: Diastolic blood pressure threshold – greater than or equal to 95 mmHg untreated people. Duration 4 years. Concurrent medication or care: taking other drugs. Indirectness: Very serious indirectness
Funding	Funding not stated (Systematic review)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: <80 mmHg TREATED versus <80 mmHg CONTROL

Protocol outcome 1: Stroke (ischaemic or haemorrhagic)
- Actual outcome for Mixed diabetic population: Stroke at 4 years; Group 1: 735/21,807, Group 2: 943/2,079
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 80–84 mmHg TREATED versus 80–84 mmHg CONTROL

Protocol outcome 1: Stroke (ischaemic or haemorrhagic)
- Actual outcome for Mixed diabetic population: Stroke at 4 years; Group 1: 393/18,780, Group 2: 516/18,736
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 85–89 mmHg TREATED versus 85–89 mmHg CONTROL Protocol outcome 1: Stroke (ischaemic or haemorrhagic) - Actual outcome for Mixed diabetic population: Stroke at 4 years; Group 1: 709/23,105, Group 2: 749/16,626 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 90–94 mmHg TREATED versus 90–94 mmHg CONTROL Protocol outcome 1: Stroke (ischaemic or haemorrhagic) - Actual outcome for Mixed diabetic population: Stroke at 4 years; Group 1: 399/19,368, Group 2: 631/19,278 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GREATER THAN OR EQUAL TO 95 mmHg TREATED versus GREATER THAN OR EQUAL TO 95 mmHg CONTROL Protocol outcome 1: Stroke (ischaemic or haemorrhagic) - Actual outcome for Mixed diabetic population: Stroke at 4 years; Group 1: 123/3,331, Group 2: 209/2,864 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness	
Protocol outcomes not reported by the study	All-cause mortality; Health-related quality of life; Myocardial infarction; Heart failure needing hospitalisation; Vascular procedures (including lower limb, coronary and carotid artery procedures); Angina needing hospitalisation; Acute kidney injury; New onset diabetes; Treatment related admission; Hypotension (dizziness)

Study	**Sheppard 2018[155]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	(n=38,286)
Countries and setting	Conducted in the UK; Setting:
Line of therapy	1st line
Duration of study	Intervention and follow up: Median follow up (FU) – 5.8 years

Study	Sheppard 2018[155]
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Mixed diabetic population
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible people were those with mild hypertension (defined as 3 consecutive blood pressure readings between 140/90–159/99 mmHg within 12 months) and low cardiovascular disease risk. Low risk people were identified by excluding anyone with a history of cardiovascular disease, left ventricular hypertrophy, atrial fibrillation, diabetes, chronic kidney disease or family history of premature heart disease. Aged between 18–74 years. Linked general practice, Hospital Episodes Statistics (HES) and Office for National Statistics (ONS) mortality records and registered to an 'up to standard' clinical practice research datalink (CPRD) practice and classified as an 'acceptable patient'.
Exclusion criteria	Anyone with a history of cardiovascular disease, left ventricular hypertrophy, atrial fibrillation, diabetes, chronic kidney disease or family history of premature heart disease. Read code for previous cardiovascular disease (stroke, myocardial infarction, angina, coronary heart disease, peripheral vascular disease, heart failure), read code for cardiovascular risk factor (left ventricular hypertrophy, atrial fibrillation, diabetes or chronic kidney disease or family history of premature heart disease), record of any blood pressure lowering medication prescription in the 12 months prior to the third consecutive blood pressure reading between 140/90–159/99 mmHg, recorded or estimated cardiovascular risk score of >20% (sensitivity analysis only). QRISK2 cardiovascular risk levels was estimated by inserting age- and sex-standardised mean cholesterol values and Townsend scores from the Health Survey for England into the algorithm to replace missing data.
Recruitment/selection of patients	Individual patient data were extracted from the medical records of all people registered at general practices contributing to the CPRD in England with linked data to the Basic Inpatient HES and ONS mortality register.
Age, sex and family origin	Age - Mean (SD): 54.8 (12). Sex (M: F): Define. Family origin: 21,283 white, 757 black, 609 south Asian, 3307 mixed family origin, 504 other, 11,826 unknown
Further population details	Mean diastolic blood pressure of 88.5 mmHg in the control group, 88.7 mmHg in the treatment group
Indirectness of population	Very serious indirectness
Interventions	(n=19,143) Intervention 1: Blood pressure threshold – 140–159 mmHg. People with blood pressure of 140–159 mmHg not treated with antihypertensives. Duration 5.8 years. Concurrent medication or care: N/A. Indirectness: No indirectness (n=19,143) Intervention 2: Blood pressure threshold – 140–159 mmHg. People with blood pressure of 140–159 mmHg treated with antihypertensives. Duration 5.8 years. Concurrent medication or care: N/A. Indirectness: No indirectness

Study	Sheppard 2018[155]
Funding	Academic or government funding. This work was funded by Medical Research Council (MRC) Strategic Skills Postdoctoral Fellowship MR/K022032/1 (Dr Sheppard), a National Institute for Health Research (NIHR) professorship (Dr Sheppard and Mr McManus), and grant NIHR-RP-R2-12-015 from the NIHR (Mr McManus). Dr Sheppard receives funding from the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health National Health Service Foundation Trust and the NIHR School for Primary Care Research (SPCR). Mr Hobbs received support from the NIHR as director of the NIHR SPCR, director of the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford, theme leader of the NIHR Oxford Biomedical Research Centre, and member of the NIHR Oxford Diagnostic Evidence Cooperative and from Harris Manchester College.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NO TREATMENT versus TREATMENT

Protocol outcome 1: All-cause mortality at Longest reported
- Actual outcome for Without type 2 diabetes: Mortality at 5.8 years; HR; 1.02 (95%CI 0.88 to 1.17);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143

Protocol outcome 2: Stroke (ischaemic or haemorrhagic) at longest reported
- Actual outcome for Without type 2 diabetes: Stroke at 5.8 years; HR; 0.97 (95%CI 0.78 to 1.21);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143

Protocol outcome 3: Myocardial infarction at Longest reported
- Actual outcome for Without type 2 diabetes: MI at 5.8 years; HR; 1.00 (95%CI 0.8 to 1.25);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143
- Actual outcome for Without type 2 diabetes: Non-MI acute coronary syndrome at 5.8 years; HR; 1.19 (95%CI 0.74 to 1.91);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143

Protocol outcome 4: Heart failure needing hospitalisation at longest reported

Study	Sheppard 2018[155]
- Actual outcome for without type 2 diabetes: Heart failure at 5.8 years; HR; 1.34 (95%CI 0.96 to 1.86); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143 Protocol outcome 5: Acute kidney injury at longest reported - Actual outcome for without type 2 diabetes: Acute kidney injury at 5.8 years; HR; 1.37 (95%CI 1 to 1.88); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143 Protocol outcome 6: Hypotension (dizziness) at longest reported - Actual outcome for without type 2 diabetes: Hypotension at 5.8 years; HR; 1.69 (95%CI 1.3 to 2.2); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: N/A; Key confounders: Age, prior CV event, smoking, sex, BP (CV risk); Group 1 Number: 19,143; Group 2 Number: 19,143	
Protocol outcomes not reported by the study	Health-related quality of life at longest reported; Vascular procedures (including lower limb, coronary and carotid artery procedures) at longest reported; Angina needing hospitalisation at longest reported; New onset diabetes at longest reported; Treatment related admission at longest reported

Study	Sundstrom 2015[162]
Study type	Systematic Review (IPD)
Number of studies (number of participants)	(n=6,361)
Countries and setting	Conducted in Multiple countries; Setting: Not specified
Line of therapy	First line
Duration of study	Intervention time: 4.4 years
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	With type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	RCTs of at least 1-year duration, people aged 18 years or older, at least 80% of whom had grade 1 hypertension and no previous cardiovascular disease, and compared an antihypertensive drug provided as

Study	Sundstrom 2015[162]
	monotherapy or a stepped care algorithm against placebo or another control regimen. We examined the available sets of trials with individual-participant data included in the BPLTTC to identify subgroups of participants meeting the review inclusion criteria. These trials also met the original inclusion criteria for participation in the BPLTTC. Data from 4 sets of comparisons were included in these analyses: angiotensin-converting enzyme (ACE) inhibitors versus placebo, calcium-channel blockers versus placebo, diuretics versus placebo, and more intensive versus less intensive blood pressure lowering regimens.
Exclusion criteria	None specified
Recruitment/selection of patients	Not specified
Age, sex and family origin	Age - Mean (SD): 63.5 years (8.4). Sex (M:F): 2544:3817. Family origin: Not stated
Indirectness of population	No indirectness
Interventions	(n=3,364) Intervention 1: Blood pressure threshold – 140–159 mmHg. Trials comparing the following were included: ACE inhibitors versus placebo, calcium-channel blockers versus placebo, diuretics versus placebo, and more intensive versus less intensive blood pressure lowering regimens. Duration 4.4 years. Concurrent medication or care: Not specified. Indirectness: No indirectness (n=2,997) Intervention 2: Blood pressure threshold – 140–159 mmHg. Trials comparing the following were included: ACE inhibitors versus placebo, calcium-channel blockers versus placebo, diuretics versus placebo, and more intensive versus less intensive blood pressure lowering regimens. Duration 4.4 years. Concurrent medication or care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (funded by the Swedish Heart-Lung Foundation, Kjell och Marta Beijers Stiftelse, and the Swedish Research Council)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 140–159 mmHg (TREATED) versus 140–159 mmHg (NOT TREATED) Protocol outcome 1: All-cause mortality - Actual outcome for With type 2 diabetes: Total deaths at 4.4 years; Group 1: 230/3,355, Group 2: 268/2,979 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness Risk of bias: All domain - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Stroke (ischaemic or haemorrhagic) - Actual outcome for with type 2 diabetes: Stroke at 4.4 years; Group 1: 230/3,052, Group 2: 267/2,845 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness Risk of bias: All domain - Low, Crossover - Low; Indirectness of outcome: No indirectness	

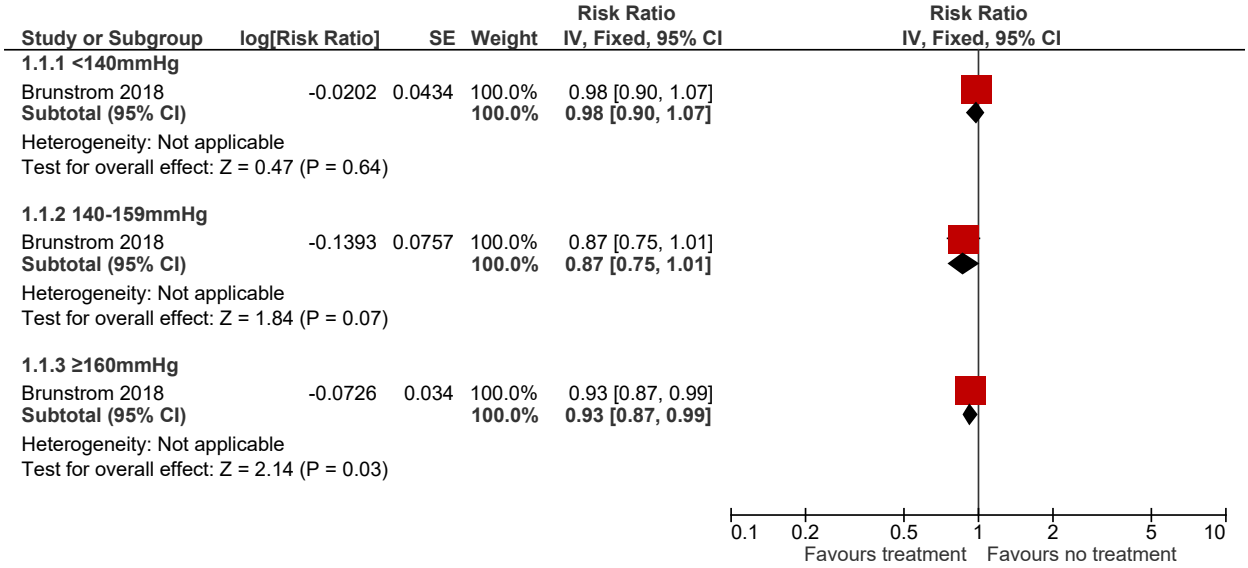
Study	Sundstrom 2015[162]
Protocol outcome 4: Heart failure needing hospitalisation - Actual outcome for with type 2 diabetes: Heart failure at 4.4 years; Group 1: 62/2,872, Group 2: 76/2,757 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Very high; Indirectness of outcome: Very serious indirectness Risk of bias: All domain - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health-related quality of life; Vascular procedures (including lower limb, coronary and carotid artery procedures); Angina needing hospitalisation; Acute kidney injury; New onset diabetes; Treatment related admission; Hypotension (dizziness)

Appendix E: Forest plots

E.1 Systolic blood pressure thresholds (mixed diabetic and non-diabetic population)

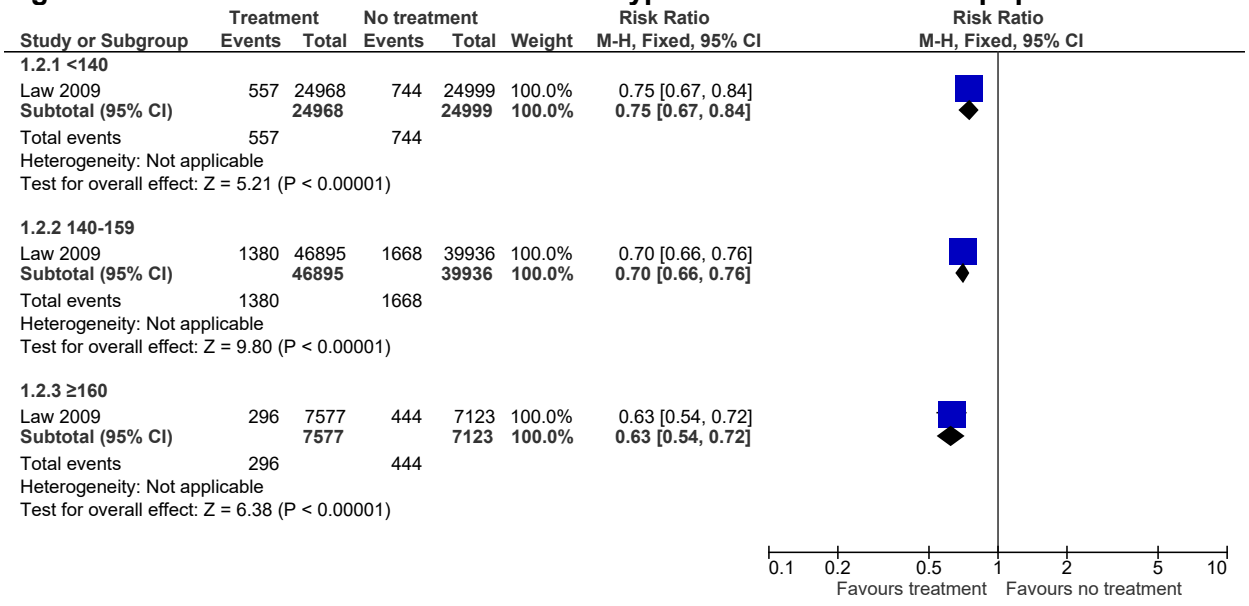
1.8.4 All-cause mortality at 4 years

Figure 3: Treatment versus no treatment in hypertensive and diabetic population



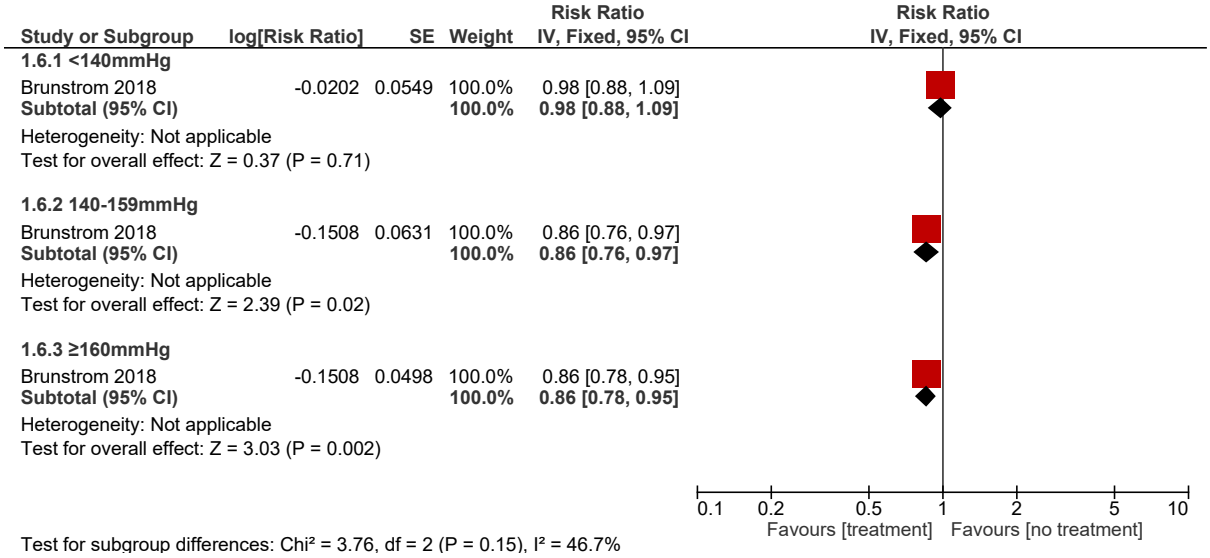
1.8.5 Stroke at 4 years

Figure 4: Treatment versus no treatment in hypertensive and diabetic population



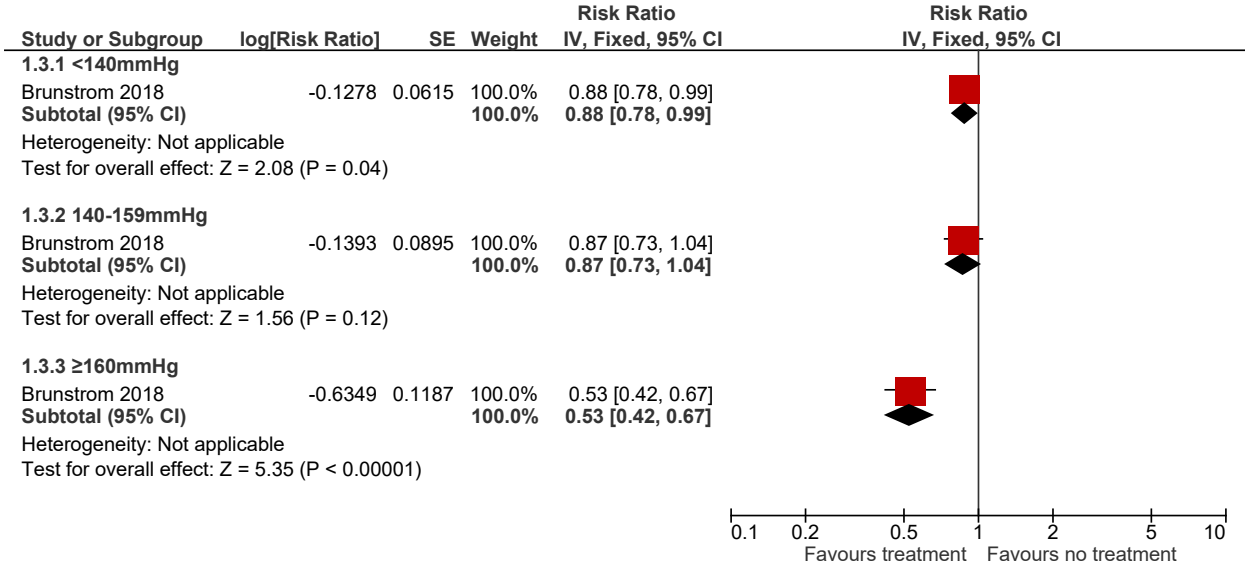
1.8.6 Coronary heart disease at 4 years

Figure 5: Treatment versus no treatment in hypertensive and diabetic population



1.8.7 Heart failure at 4 years

Figure 6: Treatment versus no treatment in hypertensive and diabetic population



E.2 Systolic blood pressure thresholds (hypertensive and type 2 diabetes strata)

Figure 7: All-cause mortality at 4.4 years

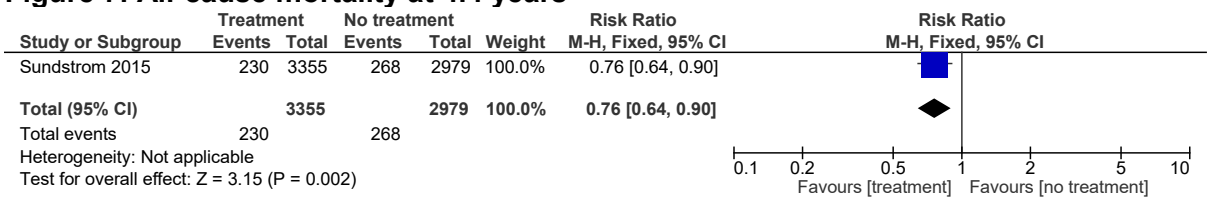


Figure 8: Stroke at 4.4 years

Study or Subgroup	Treatment Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sundstrom 2015	230	3052	267	2845	100.0%	0.80 [0.68, 0.95]
Total (95% CI)		**3052**		**2845**	**100.0%**	**0.80 [0.68, 0.95]**
Total events	230		267			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)

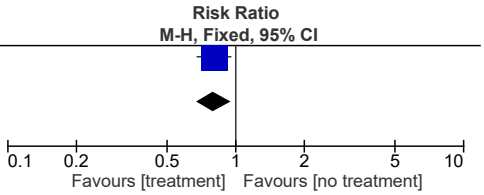
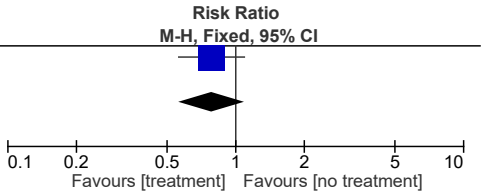


Figure 9: Heart failure at 4.4 years

Study or Subgroup	Treatment Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sundstrom 2015	62	2872	76	2757	100.0%	0.78 [0.56, 1.09]
Total (95% CI)		**2872**		**2757**	**100.0%**	**0.78 [0.56, 1.09]**
Total events	62		76			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

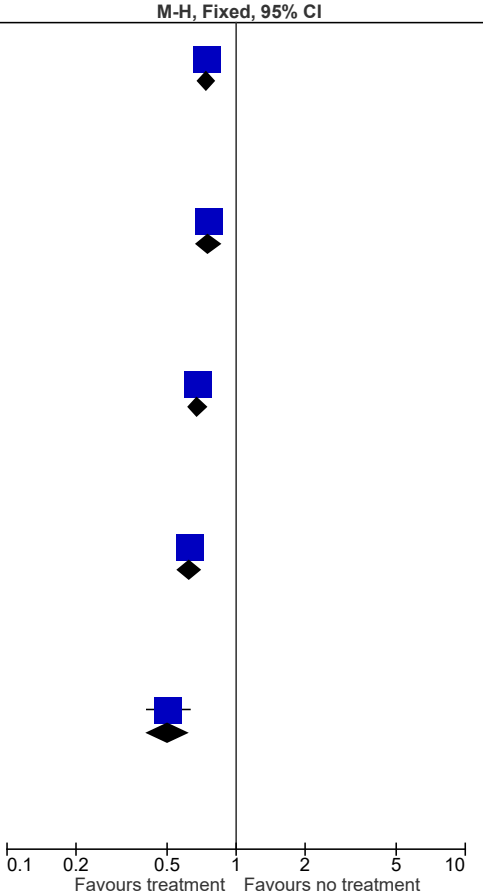


E.3 Diastolic blood pressure thresholds (mixed diabetic and non-diabetic population)

1.8.8 Stroke

Figure 10: Treatment versus no treatment in hypertensive and diabetic population

Study or Subgroup	Treatment Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 >80mmHg						
Law 2009	735	21807	943	20792	100.0%	0.74 [0.68, 0.82]
Subtotal (95% CI)		**21807**		**20792**	**100.0%**	**0.74 [0.68, 0.82]**
Total events	735		943			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.15 (P < 0.00001)						
1.7.2 80-84mmHg						
Law 2009	393	18780	516	18736	100.0%	0.76 [0.67, 0.87]
Subtotal (95% CI)		**18780**		**18736**	**100.0%**	**0.76 [0.67, 0.87]**
Total events	393		516			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.15 (P < 0.0001)						
1.7.3 85-89mmHg						
Law 2009	709	23105	749	16626	100.0%	0.68 [0.62, 0.75]
Subtotal (95% CI)		**23105**		**16626**	**100.0%**	**0.68 [0.62, 0.75]**
Total events	709		749			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.47 (P < 0.00001)						
1.7.4 90-94mmHg						
Law 2009	399	19368	631	19278	100.0%	0.63 [0.56, 0.71]
Subtotal (95% CI)		**19368**		**19278**	**100.0%**	**0.63 [0.56, 0.71]**
Total events	399		631			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.33 (P < 0.00001)						
1.7.5 >95mmHg						
Law 2009	123	3331	209	2864	100.0%	0.51 [0.41, 0.63]
Subtotal (95% CI)		**3331**		**2864**	**100.0%**	**0.51 [0.41, 0.63]**
Total events	123		209			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.15 (P < 0.00001)						



E.4 Systolic blood pressure threshold of 140–159 mmHg: treatment versus no treatment (no type 2 diabetes)

Figure 11: Mortality at 5.8 years

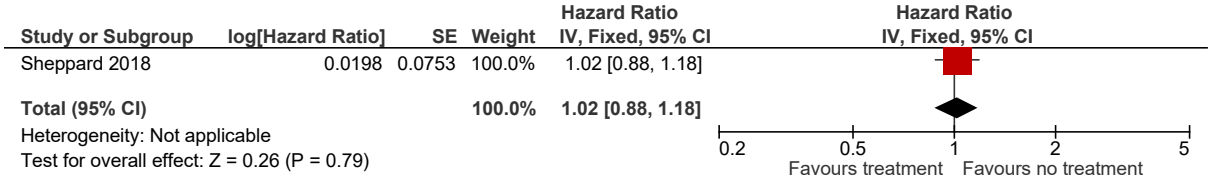


Figure 12: Stroke at 5.8 years

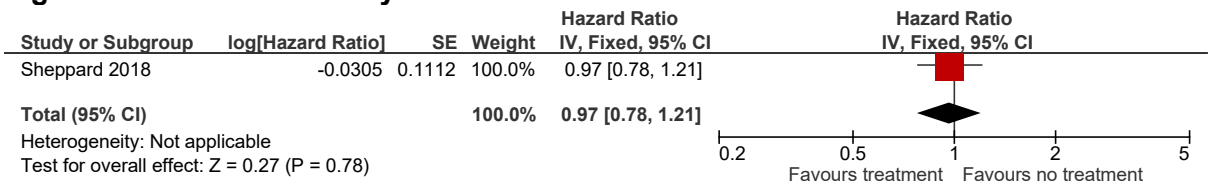


Figure 13: Myocardial Infarction at 5.8 years

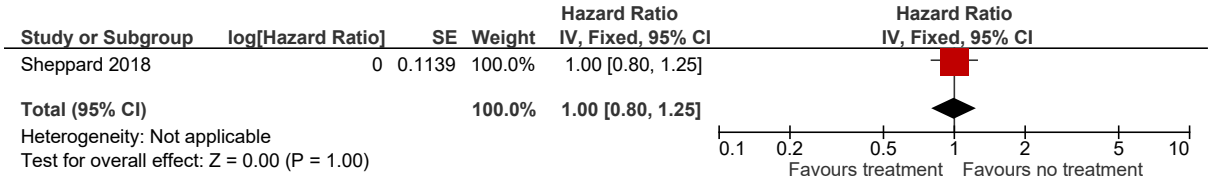


Figure 14: Heart Failure at 5.8 years

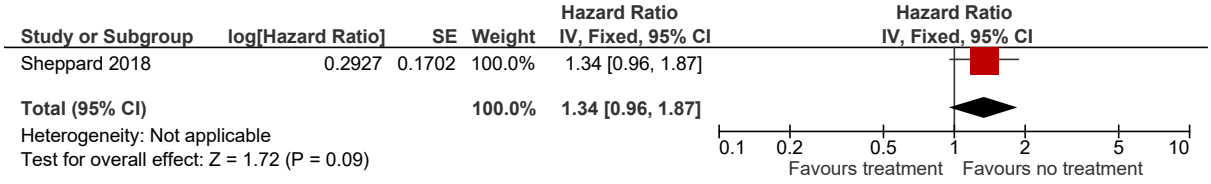


Figure 15: Non-Myocardial Infarction Acute Coronary Syndrome at 5.8 years

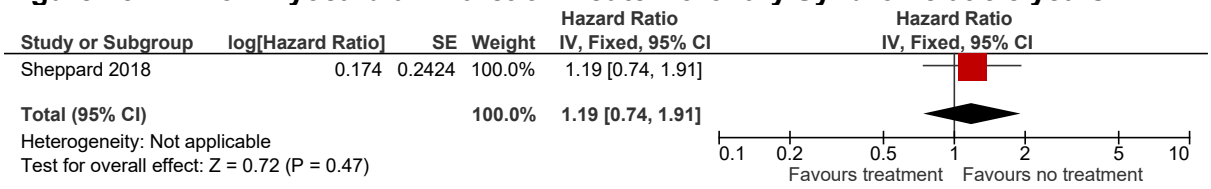


Figure 16: Hypotension at 5.8 years

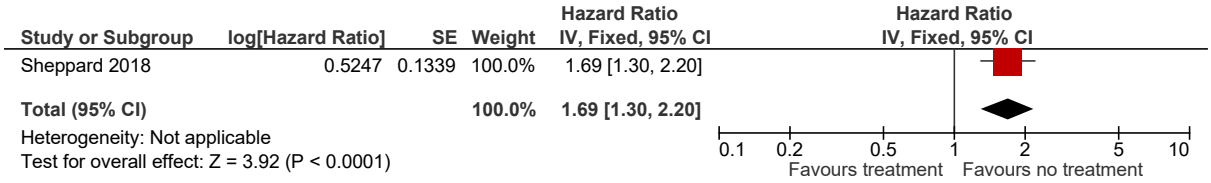
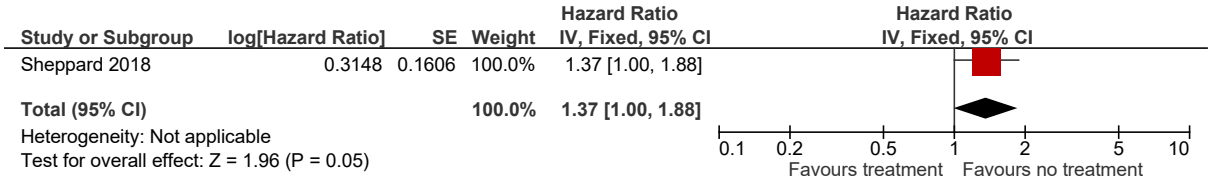


Figure 17: Acute Kidney Injury at 5.8 years



Appendix F: GRADE tables

Table 21: Clinical evidence profile: treatment versus no treatment at systolic blood pressure thresholds (with and without type 2 diabetes)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment versus no treatment	Control	Relative (95% CI)	Absolute		
All-cause mortality - <140mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	-	-	RR 0.98 (0.9 to 1.07)	[4,897 events in 68, 16 people][5]	⊕⊕OO LOW	CRITICAL
All-cause mortality - 140-159mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[1]	none	-	-	RR 0.87 (0.75 to 1.01)	7 fewer per 1000 (from 14 fewer to 1 more)[3]	⊕OOO VERY LOW	CRITICAL
All-cause mortality - ≥160mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	-	-	RR 0.93 (0.87 to 0.99)	6 fewer per 1000 (from 1 fewer to 11 fewer)[3]	⊕⊕OO LOW	CRITICAL
Stroke - <140 (follow-up mean 4 years)												

1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[1]	none	-	-	RR 0.85 (0.68 to 1.06)	4 fewer per 1000 (from 10 fewer to 2 more)[4]	⊕OOO VERY LOW	CRITICAL
Stroke - 140-159 (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[1]	none	-	-	RR 0.86 (0.72 to 1.03)	6 fewer per 1000 (from 12 fewer to 1 more)[4]	⊕OOO VERY LOW	CRITICAL
Stroke - ≥160 (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision[1]	none	-	-	RR 0.69 (0.6 to 0.79)	19 fewer per 1000 (from 13 fewer to 25 fewer)[4]	⊕⊕OO LOW	CRITICAL
Coronary heart disease - <140 mmHg (Copy; follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	no serious imprecision	none	-	-	RR 0.98 (0.88 to 1.09)	1 fewer per 1000 (from 8 fewer to 6 more)[4]	⊕⊕OO LOW	CRITICAL
Coronary heart disease - 140-159mmHg (Copy)												
1	no methodology chosen	no serious risk of bias	no serious inconsistency	Very serious[1]	serious[1]	none	-	-	RR 0.86 (0.76 to 0.97)	5 fewer per 1000 (from 1 fewer to 8 fewer)[4]	⊕OOO VERY LOW	CRITICAL
Coronary heart disease - ≥160mmHg (Copy)												
1	no methodology chosen	no serious risk of bias	no serious inconsistency	Very serious[1]	serious[1]	none	-	-	RR 0.86 (0.78 to 0.95)	8 fewer per 1000 (from 3 fewer to 12 fewer)[4]	⊕OOO VERY LOW	CRITICAL

Heart failure - <140mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[1]	none	-	-	RR 0.88 (0.78 to 0.99)	[2,261 events in 60,879 people] 5	⊕OOO VERY LOW	IMPORTANT
Heart failure - 140-159mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[1]	none	-	-	RR 0.87 (0.73 to 1.04)	[1,113 events in 35,254 people]5	⊕OOO VERY LOW	IMPORTANT
Heart failure - ≥160mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	-	-	RR 0.53 (0.42 to 0.67)	[520 events in 23,395 people]5	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment due to population or outcome indirectness or by 2 increments for both population and outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[3]Control group risk not reported; values extrapolated from Bulpitt 198838

[4]Control group risk not reported; values extrapolated from Law 200990

[5]Control group risk not reported; therefore, absolute risk could not be calculated: no data was available that values could be extrapolated from.

Table 22: Clinical evidence profile: Treatment versus no treatment at systolic blood pressure thresholds (type 2 diabetes)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Treatment**	**No treatment (diabetes)**	**Relative (95% CI)**	**Absolute**		

All-cause mortality - 140-159mmHg (follow-up mean 4.4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	230/3355 (6.9%)	268/2979 (9%)	RR 0.76 (0.64 to 0.9)	22 fewer per 1000 (from 9 fewer to 32 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - 140-159mmHg (follow-up mean 4.4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	230/3052 (7.5%)	267/2845 (9.4%)	RR 0.8 (0.68 to 0.95)	19 fewer per 1000 (from 5 fewer to 30 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Heart failure - 140-159mmHg (follow-up mean 4.4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	62/2872 (2.2%)	76/2757 (2.8%)	RR 0.78 (0.56 to 1.09)	6 fewer per 1000 (from 12 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 23: Clinical evidence profile: Treatment versus no treatment at diastolic blood pressure thresholds (with and without type 2 diabetes)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Treatment versus no treatment**	**Control**	**Relative (95% CI)**	**Absolute**		
Stroke (diastolic) - >80mmHg (follow-up mean 4 years)												

1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	735/21807 (3.4%)	943/20792 (4.5%)	RR 0.74 (0.68 to 0.82)	12 fewer per 1000 (from 8 fewer to 15 fewer)	⊕OOO VERY LOW	CRITICAL
Stroke (diastolic) - 80-84mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	393/18780 (2.1%)	516/18736 (2.8%)	RR 0.76 (0.67 to 0.87)	7 fewer per 1000 (from 4 fewer to 9 fewer)	⊕OOO VERY LOW	CRITICAL
Stroke (diastolic) - 85-89mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	709/23105 (3.1%)	749/16626 (4.5%)	RR 0.68 (0.62 to 0.75)	14 fewer per 1000 (from 11 fewer to 17 fewer)	⊕⊕OO LOW	CRITICAL
Stroke (diastolic) - 90-94mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	399/19368 (2.1%)	631/19278 (3.3%)	RR 0.63 (0.56 to 0.71)	12 fewer per 1000 (from 9 fewer to 14 fewer)	⊕⊕OO LOW	CRITICAL
Stroke (diastolic) - >95mmHg (follow-up mean 4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	123/3331 (3.7%)	209/2864 (7.3%)	RR 0.51 (0.41 to 0.63)	36 fewer per 1000 (from 27 fewer to 43 fewer)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment due to population or outcome indirectness, or by 2 increments for both population and outcome indirectness.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 24: Clinical evidence profile: Treatment versus no treatment at systolic blood pressure threshold of 140–159 mmHg (without type 2 diabetes)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	No treatment (no diabetes)	Relative (95% CI)	Absolute[3]		
Mortality - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	860/19143 (4.5%)	781/19143 (4.1%)	HR 1.02 (0.88 to 1.18)[4]	1 more per 1000 (from 5 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Stroke - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	292/19143 (1.5%)	285/19143 (1.5%)	HR 0.97 (0.78 to 1.21)[4]	0 fewer per 1000 (from 3 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Myocardial Infarction - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	276/19143 (1.4%)	279/19143 (1.5%)	HR 1 (0.8 to 1.25)[4]	0 fewer per 1000 (from 3 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Heart failure - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	169/19143 (0.88%)	131/19143 (0.68%)	HR 1.34 (0.96 to 1.87)[4]	2 more per 1000 (from 0 fewer to 6 more)	⊕OOO VERY LOW	IMPORTANT
Non-MI acute coronary syndrome - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	very serious[2]	none	61/19143 (0.32%)	56/19143 (0.29%)	HR 1.19 (0.74 to 1.91)[4]	1 more per 1000 (from 1 fewer to 3 more)	⊕OOO VERY LOW	IMPORTANT
Hypotension - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	268/19143 (1.4%)	161/19143 (0.84%)	HR 1.69 (1.3 to 2.2)[4]	6 more per 1000 (from 3 more to 10	⊕OOO	IMPORTANT

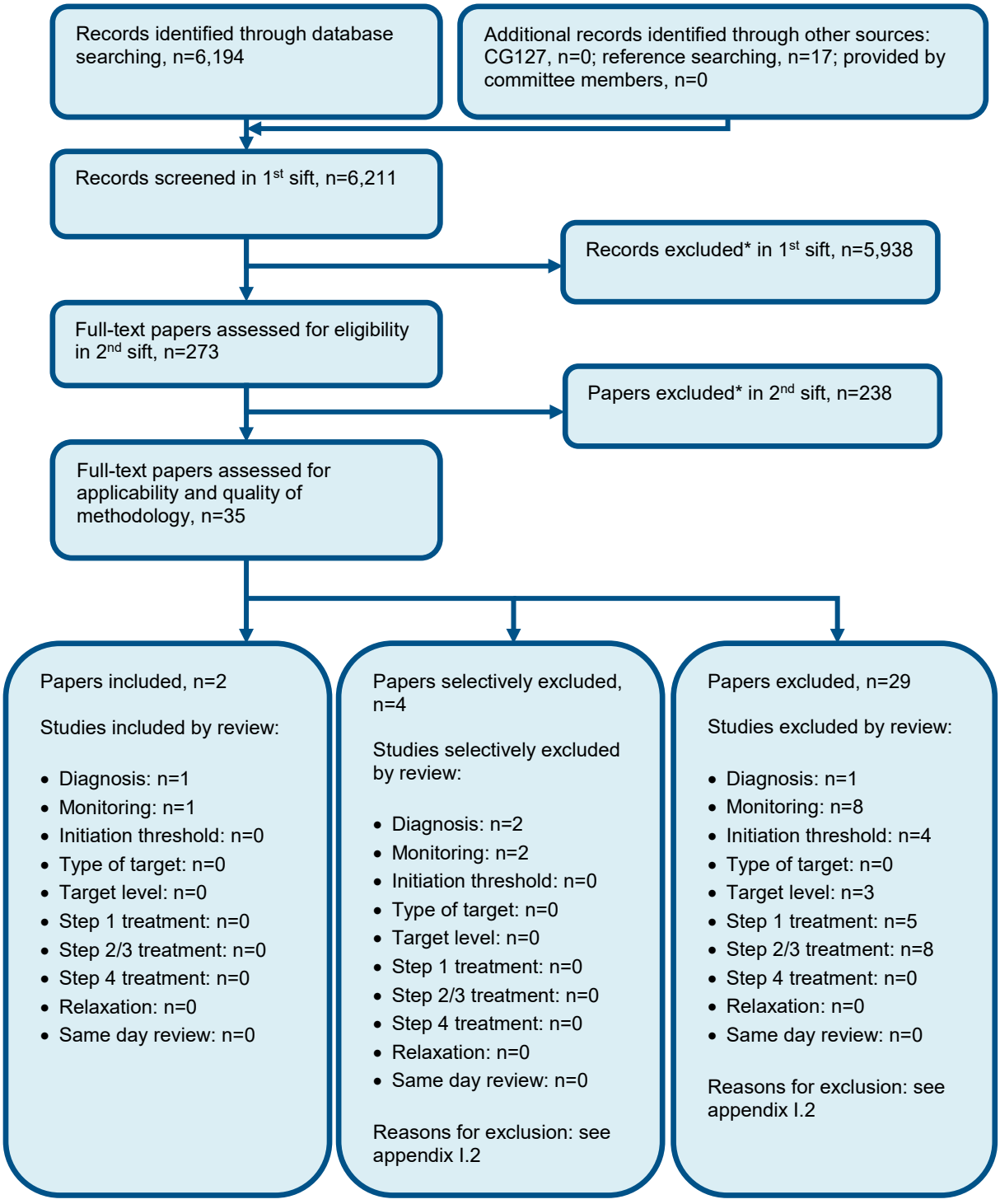
										more)	VERY LOW	
Acute Kidney Injury - 140-159mmHg (follow-up median 5.8 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	194/19143 (1%)	144/19143 (0.75%)	HR 1.37 (1 to 1.88)[4]	3 more per 1000 (from 0 more to 7 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3]Absolute effects calculated by inputting raw event data from median follow up time into GRADE.

[4]Evidence based on one study that reported HRs with raw event data.

Appendix G: Health economic evidence selection

Figure 18: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 25: Studies excluded from the clinical review that were included in the previous guideline (CG127)

Study	Exclusion reason
Arima 2006[10]	Study took place prior to 2000 date cut off
Arima 2009[11]	Incorrect population (not treated)
Asayama 2009[17]	Incorrect population (not hypertension), study design and analysis
Assmann 2005[20]	No relevant outcomes, incorrect comparison. Prognostic study predicting cardiovascular outcomes based on pulse pressure.
Barengo 2009[25]	Incorrect comparison, incorrect analysis
Barengo 2009[26]	Incorrect study design, incorrect population. Population included normotensive people and compared cardiovascular risk between groups.
Benetos 2003[29]	Incorrect comparison. Comparing people with hypertension to normotensive people.
Borghi 2003[35]	Incorrect study design, incorrect interventions. Not comparing treatment initiation thresholds. Study comparing link between systolic and diastolic blood pressure with cardiovascular outcomes.
Britton 2009[38]	Incorrect population; including people with heart failure
Carlsson 2009[47]	Study took place prior to 2000 date cut off
Conen 2007[49]	Incorrect comparison. Comparing people with hypertension to normotensive people.
Deckers 2006[51]	Incorrect population
Fagard 2007[61]	Incorrect comparison. Study did not compare initation of treatment at different blood pressure thresholds
Fagard 2004[60]	Incorrect study design. Comparing ambulatory and clinic blood pressure measurements as predictors of cardiovascular events
Fang 2006[62]	Incorrect comparison. Comparing risk of stroke in hypertensive and nomotensive people.
Gustavsen 2003[76]	Incorrect population; white coat hypertension only
Haider 2003[77]	Incorrect study design. Prognostic study comparing predictive value of systolic blood pressure, diastolic blood pressure and pulse pressure for the onset of congestive heart failure.
Head 2010[80]	Incorrect comparison, incorrect study design. Correlations between ambulatory and clinic blood pressure.
Inoue 2007[86]	Incorrect study design. Prognostic study comparing predictive value of systolic blood pressure amd diastolic blood pressure for predicting cardiovascular events
Ishikawa 1997[89]	Incorrect analysis
Kagiyama 2008[96]	Study took place prior to 2000 date cut off
Kokubo 2008[101]	Incorrect comparison
Kono 2005[102]	Incorrect comparison. Class comparison of different drugs, comparing

Study	Exclusion reason
	the effect on cardiovascular events (case-control study).
Kshirsagar 2006[103]	Incorrect population. Population had a blood pressure below the diagnsotic threshold for hypertension
Obara 2007[139]	Incorrect comparison. Comparing predictive value of systolic and diastolic blood pressure for cardiovascular outcomes.
Okayama 2006[143]	Study took place prior to 2000 date cut off. Incorrect comparison; comparing predictive value of systolic and diastolic blood pressure for cardiovascular outcomes
Sairenchi 2005[153]	Incorrect study design. Prognostic study comparing predictive value of systolic blood pressure and diastolic blood pressure for the onset of mortality
Weitzman 2005[186]	Incorrect comparison, incorrect population. Comparing people with normotensive blood pressure to people with hypertension

Table 26: Studies excluded from the clinical review

Study	Exclusion reason
Adamsson Eryd 2016[1]	Incorrect study design, Incorrect population
Akanabe 1985[2]	Before 2000; incorrect analysis
ALLHAT collaborate research group 2000[3]	Incorrect comparison
Ambrosius 2014[4]	Incorrect comparison
Anand 2007[6]	Incorrect population (heart failure)
Anand 2008[5]	Incorrect population (heart failure)
Anavekar 2004[7]	No relevant outcomes
Anderson 2011[8]	Incorrect study design
Anon 2014[9]	Abstract
Arima 2006[10]	Study took place prior to 2000 date cut off
Arima 2009[11]	Incorrect population (not treated)
Arnold 2003[12]	Incorrect analysis
Asayama 2009[17]	Incorrect population, study design and analysis
Asayama 2012[15]	No relevant outcomes
Asayama 2014[18]	Incorrect population, study design and analysis
Asayama 2014[19]	Incorrect population
Asayama 2016[14]	No relevant outcomes
Asayama 2017[13]	No relevant outcomes, Incorrect comparison, incorrect population
Asayama 2018[16]	Already treated at baseline
Assmann 2005[20]	No relevant outcomes, incorrect comparison
Aydogan 2015[22]	Already treated at baseline
Baker 2000[23]	No relevant outcomes
Banach 2014[24]	Incorrect study design
Barengo 2009[26]	Incorrect study design, incorrect population
Barengo 2009[25]	Incorrect comparison, incorrect analysis
Beckett 2014[27]	Included in systematic review
Benavente 2013[28]	Incorrect analysis (not adjusted)
Benetos 2003[29]	Incorrect comparison
Blacher 2000[30]	Incorrect population

Study	Exclusion reason
Black 2003[31]	Incorrect comparison, no relevant outcomes
Blood Pressure Lowering Treatment Trialists 2008[32]	Incorrect comparison
Bohm 2016[33]	Incorrect population
Borghi 2003[35]	Incorrect study design, incorrect interventions
Borghi 2004[34]	No relevant outcomes, data set before 2000
Boutitie 2002[36]	No relevant outcomes
Brimble 2016[37]	Not article
Britton 2009[38]	Incorrect population
Brown 2000[39]	Incorrect population, Incorrect comparison
Bulpitt 2001[42]	Incorrect population
Bundy 2017[44]	Conference abstract
Bundy 2017[45]	Incorrect comparison
Butler 2011[46]	Incorrect population
Carlsson 2013[47]	Study took place prior to 2000 date cut off
Conen 2007[49]	Incorrect comparison
Czernichow 2011[50]	Incorrect population, incorrect comparison, incorrect study design
Deckers 2006[51]	Incorrect population
Derosa 2014[52]	Incorrect comparison
Derosa 2014[53]	Article retracted
Dregan 2016[54]	Incorrect analysis
Estacio 2006[56]	Incorrect comparison
Ettehad 2016[57]	Systematic review; references checked
Fagard 1999[59]	Study took place prior to 2000 date cut off
Fagard 2004[60]	Incorrect study design
Fagard 2007[61]	Incorrect comparison.
Fagard 2007[58]	Incorrect population
Fang 2006[62]	Incorrect comparison
Feldstein 2014[63]	Incorrect population
Ferrucci 2001[65]	Incorrect analysis
Filippi 2010[66]	No relevant outcomes
Freitag 2003[67]	Review, references checked
Frontoni 2014[68]	Commentary
Fuchs 2011[69]	Protocol
Fuchs 2016[70]	Included in systematic review
Garrison 2017[71]	Incorrect comparison
Geraci 2003[72]	Incorrect population
Grassi 2016[73]	Literature review
Gueyffier 1997[75]	No relevant outcomes
Gueyffier 1999[74]	Study took place prior to 2000 date cut off
Gustavsen 2003[76]	Incorrect population
Haider 2003[77]	Incorrect study design
Hansen 2007[78]	Study took place prior to 2000 date cut off
Hara 2014[79]	Incorrect population
Head 2010[80]	Incorrect comparison, incorrect study design

Study	Exclusion reason
Ho 2018[81]	Incorrect comparison
Hong 2018[82]	Systematic review, references checked
Howard 2008[83]	Incorrect comparison
Huse 2000[84]	Incorrect study design
In der Schmitten 2013[85]	Incorrect study design
Inoue 2007[86]	Incorrect study design
Isezuo 2003[87]	Incorrect population
Ishikawa 2008[88]	Incorrect analysis
Izzo 2011[90]	Review; references checked
Jacobs 2017[91]	Incorrect comparison
JATOS study group 2008[93]	Incorrect interventions
Johnson 1993[94]	incorrect population
Julius 2006[95]	No useable outcomes
Kagiyama 2008[96]	Study took place prior to 2000 date cut off
Kalkman 2017[97]	Meta-analysis; references checked
Karmali 2017[98]	Incorrect comparison
Kengne 2009[99]	No useable outcomes
Kim 2013[100]	No relevant outcomes
Kokubo 2008[101]	Incorrect comparison
Kono 2005[102]	Incorrect comparison
Kshirsagar 2006[103]	Incorrect population
Ku 2018[104]	Incorrect population
Lachouri 2009[106]	No relevant outcomes
Le 2017[108]	No relevant outcomes
Lee 2012[109]	No relevant outcomes
Li 2005[110]	Incorrect population
Li 2014[112]	Abstract
Li 2016[111]	Adjusted for treatment
Lithell 2003[113]	Incorrect study design
Liu 2009[115]	Included studies before cut off 2000
Liu 2015[114]	Incorrect population
Lonn 2016[117]	Incorrect population, no relevant outcomes, incorrect interventions
Lonn 2016[116]	Incorrect population, no relevant outcomes, incorrect interventions
Lopez-Paz 2010[118]	Abstract
Luders 1002[119]	No relevant outcomes
Lund Haheim 1995[120]	Study took place prior to 2000 date cut off
Ma 2012[121]	Inappropriate washout period
MacMahon 2001[122]	Incorrect population
Mancia 2016[123]	Incorrect comparison
Margolis 2014[124]	Incorrect population
Mariampillai 2016[125]	Commentary
Mehlum 2018[126]	No useable data
Meredith 2008[128]	Incorrect population
Meredith 2016[127]	Incorrect comparison

Study	Exclusion reason
Moraes 2017[129]	Systematic review, references checked
Muntner 2017[130]	No relevant outcomes
Myers 2016[131]	Incorrect comparison
Nakamura 2006[132]	Study took place prior to 2000 date cut off
Nelson 2015[135]	Incorrect analysis
Ninomiya 2008[136]	Incorrect population
Nissen 2004[137]	Incorrect comparison
Ntaios 2011[138]	No useable data
Obara 2007[139]	Incorrect comparison
Ogihara 2008[140]	Incorrect comparison
Ogihara 2010[141]	Incorrect population (already treated)
Ohkuma 2017[142]	No relevant outcomes
Okayama 2006[143]	Study took place prior to 2000 date cut off. Incorrect comparison
Papademetriou 2016[144]	Incorrect comparison
Patel 2007[145]	Incorrect comparison
Patel 2017[146]	No relevant outcomes
Pocock 2001[147]	Study took place prior to 2000 date cut off
Pringle 2003[148]	Incorrect interventions
Redon 2012[149]	Incorrect study design
Remme 2009[150]	Incorrect analysis
Rouleau 2004[151]	No relevant outcomes
Ruggenenti 2012[152]	Incorrect study design
Sairenchi 2005[153]	Incorrect study design
Shapiro 2018[154]	Incorrect comparison
Shiraishi 2012[157]	Incorrect population
Singh 2012[158]	Conference abstract
Sipahi 2012[159]	Systematic review, references checked
Sleight 2009[160]	Order cancelled
Sundstrom 2013[164]	Incorrect population
Sundstrom 2014[163]	Incorrect study design
Takase 2017[165]	Incorrect study design
The ADVANCE Collaborative Group 2001[166]	Incorrect interventions; incorrect analysis
Thomopoulos 2014[167]	Systematic review, references checked
Thomopoulos 2014[169]	Systematic review, references checked
Thomopoulos 2016[168]	Incorrect comparison
Thomopoulos 2017[170]	Incorrect comparison
Thomopoulos 2018[171]	Systematic review, references checked
Thompson 2011[172]	Incorrect analysis
Tiessen 2013[173]	Incorrect interventions
Tillin 2011[174]	Incorrect population
Turnbull 2005[175]	Systematic review, references checked
Ueshima 2003[176]	Study took place prior to 2000 date cut off
Veloudi 2016[177]	No relevant outcomes
Verdecchia 2009[178]	Incorrect population (already treated)
Vishram 2015[179]	No relevant outcomes

Study	Exclusion reason
Wan 2017[180]	incorrect study design, incorrect study population
Wan 2017[181]	No relevant outcomes
Wang 2005[182]	Incorrect comparison
Webb 2010[183]	No relevant outcomes
Weber 2010[185]	No relevant outcomes
Weber 2013[184]	Incorrect comparison
Weitzman 2005[186]	Incorrect comparison
Wing 2003[187]	Before cut off of 2000; previously treated
Wong 2013[188]	No relevant outcomes
Xie 2016[189]	Incorrect population; incorrect analysis
Yui 2004[190]	Incorrect comparison
Yusuf 2009[192]	Incorrect comparison
Yusuf 2012[193]	Less than minimum duration; Incorrect comparison
Yusuf 2016[191]	Incorrect population, no relevant outcomes, incorrect interventions
Zamorano 2011[194]	No relevant outcomes
Zanchetti 2003[195]	Incorrect comparison
Zheng 2015[196]	Incorrect comparison

I.2 Excluded health economic studies

Table 27: Studies excluded from the health economic review

Reference	Reason for exclusion
Athanasakis 2011[21]	This study was assessed as partially applicable with very serious limitations because although it is comparing treatment versus no treatment in a hypertensive population, the treatment effect is based on observational systolic BPs in a treated and untreated group being put into a risk calculator as above.
Ferket 2017[64]	This study was assessed as not applicable because the intervention that is being compared in different CV risk subgroups is a polypill that also includes a statin.
Kypridemos 2018[105]	This study was assessed as not applicable because it is comparing different types of implementation of NHS health check, which can lead to identification of many conditions and not just hypertension, so it is not just about antihypertensive treatment.
Stevanovic 2014[161]	This study was assessed as partially applicable with very serious limitations because although it is comparing treatment versus no treatment in a hypertensive population, it uses a different risk calculator to what would be used in the UK. It also uses BP reduction for treatment effect (rather than a relative risk reduction in events) and predicts events through the calculator which should ideally be used only for baseline risks. It also has different treatment steps to UK practice.

Appendix J: Research recommendations

J.1 Threshold interventions

Research question: In adults aged under 40 with hypertension (with or without type 2 diabetes), what are the appropriate risk and blood pressure thresholds for starting treatment?

Why this is important:

There is uncertainty about how to assess the impact of blood pressure treatment in people aged under 40 with stage 1 hypertension and no overt target organ damage or cardiovascular disease. Although it is inevitable that those with untreated hypertension will develop premature target organ damage over the many years and decades they are affected, it is unclear at what level of 10-year or lifetime vascular risk pharmacological treatment of hypertension in those aged under 40 will be cost effective. The economic model in this guideline suggests that treating stage 1 hypertension is cost effective at lower levels of 10-year risk in younger people than in older people. The 10-year Q-RISK2 risk at which treatment of 40 year olds with stage 1 hypertension without target organ damage is cost effective at the minimal willingness to pay threshold of £20K per QALY using probabilistic ICERs, is as low as 0.83% (males) and 1.86% (females).This implies that all 40-year-old males with uncomplicated stage 1 hypertension should be offered treatment since their cardiovascular risk is typically greater than this threshold.

Cost effectiveness of treating those aged under 40 is a key issue for regional specialist hypertension services, the many affected people and the wider NHS. It is recognised that longer than usual follow up will be required to answer this question with hard outcomes including all-cause mortality, heart attack and stroke.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People with hypertension aged under 40 with or without target organ damage (stratified by BP or cardiovascular risk). Intervention(s): Lifestyle and pharmacological interventions to lower blood pressure. Comparison: Lifestyle intervention with no antihypertensive treatment. Outcome(s): All-cause mortality, myocardial infarction, stroke and health related quality of life.
Importance to patients or the population	An increasing number of people are recognised to have hypertension whose onset occurs at aged under 40. The lifetime cardiovascular risk to people and health cost to the NHS of this phenomenon is currently poorly characterised.
Relevance to NICE guidance	High quality research in this area may enable future updates of this guidance to make a strong recommendation on the cost utility thresholds at which treatment of people aged under 40 is beneficial.
Relevance to the NHS	People with a young onset of hypertension have often more than 50 years of life during which treatment may be effective, and the NHS has more than half a century of health costs to meet per affected individual. It seems likely that cheap effective treatment early on may reduce lifetime healthcare cost to the NHS from vascular events.
National priorities	Balancing the health needs of the young is important since most treatments in cardiovascular disease are focused on the elderly.
Current evidence base	Hypertension in adults 2019 NICE guideline update of CG127: no evidence specific to people aged under 40 was identified in the evidence review included in this guideline.
Equality	None.

Study design	A long-term follow up of an RCT with people randomised to treatment (randomisation to 'A' versus 'C' drugs) plus lifestyle advice versus lifestyle advice only.
Feasibility	Realisation from funders that such an important issue requires longer than usual follow up for vascular outcomes and all-cause mortality. Multiple funders may be required to share the risks of a long-term study.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline. This issue will affect the UK population indefinitely and so answering it as soon as possible, even if that takes a decades-long study, is a good use of limited resources.