National Institute for Health and Care Excellence

Final

Hypertension in adults (update)

[K] Evidence summary for pharmacological treatment in CVD

NICE guideline NG136

Evidence underpinning recommendation 1.4.31

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Final

This evidence report was developed by the National Guideline Centre

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1.1 Clinical question

Should the choice of antihypertensive therapy be different in adults with hypertension and established cardiovascular disease, compared to those without established cardiovascular disease, and does this vary with age or ethnicity?

1.1.1 Introduction

Pharmacological treatment of hypertension for people with pre-existing cardiovascular disease

Most individuals on treatment for hypertension are prescribed more than 1 medication to achieve their target blood pressure. One of the reasons for this is that different medications act on different pathways of blood pressure regulation. When 1 pathway is modified by a medication, the other pathways may compensate to keep the blood pressure elevated. The guideline therefore recommends a treatment algorithm with 4 steps for people with hypertension. A mapping exercise carried out across NICE guidelines identified this as a gap in recommendations.

A number of factors require consideration: People with pre-existing cardiovascular disease coming into the hypertension treatment pathway may already be on 1 of the drugs recommended in the algorithm; there may be condition-specific considerations which make the use of a particular drug inappropriate; evidence from previous guidelines may indicate a preference for a different choice of drug for people who have had a particular cardiovascular condition. These issues will be considered within this chapter.

1.1.2 Methods and process

This report was developed using the methods and process described in Developing NICE guidelines: the manual. Declarations of interest were recorded according to NICE's conflicts of interest policy.

As stated in the scope for the update of this guideline, a new systematic review was not prioritised for this area. No protocol was developed and neither were new literature searches undertaken. Instead, the existing evidence reviews in previous versions of the guideline were agreed to be examined for evidence on people with cardiovascular disease to inform recommendations. Protocols and search strategies from previous versions of the guideline can be found in the relevant appendices of NG136.

This report was quality assured by a senior systematic reviewer. This included checking:

- papers were included or excluded appropriately
- a sample of the data extractions
- a sample of the risk of bias assessments
- correct methods were used to synthesise data.

Discrepancies were identified and resolved through discussion (with a third reviewer where necessary).

The aim of this report was to determine whether the existing recommendations are generalisable to the cardiovascular disease (CVD) population, or if separate recommendations are required. For the purposes of this report, established CVD includes past medical history of:

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

Synthesis of the clinical evidence

The strategy taken was to re-evaluate all studies included in the previously published versions of the NICE guideline on hypertension in adults that related to pharmacological treatments.

Firstly, all previously included studies were assessed to determine:

- the proportion of adults with established CVD, and
- whether or not there was a subgroup analysis for those with versus without established CVD.

Secondly, more detailed re-examination of the evidence was undertaken for studies that met one of 2 criteria.

1. **Studies with subgroup data for outcomes in those with and without CVD**

Subgroup data were used to inform whether there was an interaction between CVD at baseline and the relative effects of treatments. These data were newly extracted for this report and were assessed and analysed in accordance with the 2019 guideline (NG136) review protocol. This included the following outcomes:

- All-cause mortality
- Health-related quality of life
- Stroke (ischaemic or haemorrhagic)
- Myocardial infarction (MI)
- Heart failure needing hospitalisation
- Vascular procedures (including both coronary and carotid artery procedures)
- Angina needing hospitalisation
- Discontinuation or dose reduction due to side effects
- 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].

Interaction statistics were taken from the studies when reported as well as being calculated in Cochrane Review Manager (RevMan5[91]) software based on a test for heterogeneity between subgroups. An I^2 statistic was computed for subgroup differences as a measure of interaction. This describes the percentage of the variability in effect estimates from the different subgroups that is due to genuine subgroup differences rather than sampling error

(chance). The p value for this I^2 statistic was used to determine whether there was a statistically significant interaction, with p≤0.05 being used as the test for significance.

Custom GRADE tables were used to present the evidence on subgroup interactions and forest plots are presented with the subgroup totals included so that the test for subgroup interactions is displayed (see methods chapter for explanation of the GRADE process).

2. Studies in exclusively CVD populations

These data were re-presented using outcomes and assessments taken from previously published versions of the NICE guideline on hypertension in adults. Withdrawal from treatment was not included in the outcome analysis because it was not originally meta-analysed owing to potential variability or subjectivity of recording. Therefore, this has been included as narrative information in the study summaries only. Similarly, from the 2004 guideline, the data on blood pressure achieved, percentage on monotherapy at the end of the trial and percentage achieving the target blood pressure were not subject to meta-analysis in this report because they were not analysed originally and do not represent clinical end-points that would be informative for recommendations.

Only data from studies that met one of these 2 above criteria are presented in evidence summaries, with further detail in the evidence tables (Appendix A), forest plots (Appendix B) and GRADE tables (Appendix C).

Details of the evidence from the remaining studies included in previous guideline versions can be found in NG136 and in the 2011, 2006 and 2004 versions.

Synthesis of economic evidence

Previously included economic evaluations and original models were also checked to determine if they contained information about whether cost effectiveness might be different in people with hypertension and established CVD:

- Did the population of the economic evaluation include people with established CVD and if so what was the proportion?

If the population was mixed, was subgroup analysis undertaken looking at cost effectiveness specifically in people with and without established CVD?

1.1.3 Summary of the NICE hypertension guideline history of pharmacological treatment reviews

Antihypertensive drug recommendations have evolved iteratively over the various versions of the hypertension guideline (2004, 2006, 2011, and 2019). Table 1 outlines the characteristics of each of the previous reviews, including whether people with established cardiovascular disease were included.

Table 1: Characteristics of antihypertensive drug reviews in NICE guidelines

Guideline	Review questions	Inclusion criteria	Outcomes	Population criteria in review	Cost-effectiveness evidence
CG18 2004 (Section 10.1, p187)	What interventions do I offer, and in what order? [35 studies – 20 placebo controlled, 15 head-to-head]	Parallel-group RCTs, analysing major cardiovascular endpoints on an intention-to-treat basis, of 1 year or more duration and enrolling 200 or more patients.	Not prespecified. Meta-analysis reported for: All-cause mortality Fatal or non-fatal MI Fatal or non-fatal stroke Withdrawal from treatment Data extracted for: All-cause mortality Coronary heart disease events Cerebrovascular events Cardiovascular events Blood pressure achieved Withdrawal % on monotherapy at end of trial % achieving target BP	Patients who had raised average blood pressure defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥85 mmHg. “Include patients both with and without cardiovascular disease and thus are relevant to the management of raised blood pressure in all of these patients after any disease specific care has been delivered.”	No EEs included[a]
CG34 2006 pharma update	Optimal sequencing of drug treatment for hypertension, using evidence from head-to-head trials (not placebo controlled)	RCTs of 1 year or more duration and enrolling 200 or more patients.	Prespecified: Mortality from any cause Stroke (ischaemic or haemorrhagic)		No EEs included[a] Cost-effectiveness modelling of first-line antihypertensive

Guideline	Review questions	Inclusion criteria	Outcomes	Population criteria in review	Cost-effectiveness evidence
(Section 10.2, p194)	[4 new studies]	Head to head only (except for isolated SH, where placebo controlled also included) Comparing any combination of antihypertensive drugs from among the following five classes of drugs: ACE inhibitors (ACEi) angiotensin-II receptor antagonists (ARB) beta-receptor blockers (BB) calcium-channel blockers (CCB) thiazide-type diuretics (TD).	Myocardial infarction (including, where reported, silent MI) Heart failure New-onset diabetes mellitus Vascular procedures (including both coronary and carotid artery procedures) Incidence of unstable angina (or angina episodes requiring hospitalisation) Study drug withdrawal.		treatment in people without pre-existing CVD, heart failure or diabetes. (Section 10.4, p228 & Appendix I p404)
CG127 2011 update (section 10.3 p 199)	1. In adults with primary hypertension, which is the most clinically and cost effective anti-hypertensive monotherapy (ACEi vs ARB) for first-line treatment, and does this vary with age and ethnicity? [3 studies] 2. In adults with primary hypertension, which is the most clinically and cost effective thiazide diuretic (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment, and does this vary with age and ethnicity? Thiazide vs other/placebo [14	RCTs with: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had chronic kidney disease (CKD). Thiazide vs other class or vs placebo: RCTs with: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD. Thiazide vs thiazide: no restrictions on sample size or follow up, cross-over included	Effectiveness • Mortality from any cause • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials)		1. No EEs included 2. No EEs included 3. No EEs included 4. No EEs included 5. 1 EE included 6. No EEs included Limited update of 2006 cost-effectiveness model of first-line antihypertensive treatment in people without pre-existing CVD, heart failure or diabetes.(Section 10.4, p228 & Appendix I p404) • Drug costs • Relative risks for ARBs updated based

Guideline	Review questions	Inclusion criteria	Outcomes	Population criteria in review	Cost-effectiveness evidence
	studies] thiazide vs thiazide [15 studies] 3. In adults with primary hypertension, which is the most clinically and cost effective combination of anti-hypertensives (A+C or A+D) for second line treatment, and does this vary with age and ethnicity? [1 study] 4. In adults with resistant hypertension, which is the most clinically and cost effective fourth-line pharmacological treatment, and does this vary with age and ethnicity? [6 cohort studies] 5. In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in elderly people (aged ≥80 years)? [2 systematic reviews, based on 8 RCTs] 6. In adults with primary hypertension, what is the most clinically and cost effective	RCTs with: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD. RCTs or cohort studies with: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD. RCTs and subgroups of RCTs with: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD. RCTs, sub-group analyses of RCTs, or cohort studies with: ≥12 months follow-up, N≥1000 per arm and the population did not consist of people who were exclusively diabetic or had CKD.	• Major adverse cardiac and cerebrovascular events (MAACE): fatal and non-fatal MI, fatal non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation (AND DIFFERENT COMPOSITES OF THIS OUTCOME) • [For comparison of diuretics vs diuretics only: BP lowering] Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioedema in black people of African and Caribbean descent		on new ACEi vs ARB data

Guideline	Review questions	Inclusion criteria	Outcomes	Population criteria in review	Cost-effectiveness evidence
	first-line anti-hypertensive treatment (drug classes) in black people of African or Caribbean descent)? [2 subgroups from RCTs]				
NG136 2019 update (see NG136; and NICE flow chart)	1. Is monotherapy or combination antihypertensive therapy more clinically and cost effective for step 1 treatment for hypertension in adults? [3 studies] 2. What is the most clinically and cost effective sequence for step 2 and step 3 treatment for hypertension in adults? [0 studies] 3. What is the most clinically and cost-effective step 4 antihypertensive drug treatment for hypertension in adults? [0 studies]	RCTs or systematic reviews with: ≥12 months follow-up. Searched all years Exclusions: type 1 diabetes or chronic kidney disease, crossover trials (unless washout is ≥ 4 weeks)	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 • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Changes in eGFR or creatinine • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the	Adults (over 18 years) with primary hypertension (with and without type 2 diabetes) Excluded people with established cardiovascular disease.	1. No EEs included 2. No EEs included 3. No EEs included No cost-effectiveness modelling undertaken.

Guideline	Review questions	Inclusion criteria	Outcomes	Population criteria in review	Cost-effectiveness evidence
			absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]		
2021 update	Scope question: What are the most clinically and cost-effective drug combinations in adults with established cardiovascular disease who require further blood pressure lowering, and does this vary with age or ethnicity? Edited review question: Should the choice of antihypertensive therapy be different in adults with hypertension and established cardiovascular disease, and does this vary with age or ethnicity?	No new reviews Any information on those with hypertension and established CVD from previously included studies	Outcomes as per original guideline reviews	Adults with established CVD from previously included evidence Any subgroup analyses reported within previously included studies to be extracted (including interaction term for the subgroups) Summarise how many studies included a CVD or CVD/non-CVD mixed population – how generalisable are the existing recommendations to the CVD population	No new reviews or modelling. The relevance of previous economic evidence to a population with hypertension and CVD will be considered.

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; EE = economic evaluation; MI = myocardial infarction; RCT = randomised clinical trial
(a) Based on evidence summarised in 2011 full guideline report that included evidence from the 2004 and 2006 iterations of the guideline.

Please see Appendix F for a summary of pharmacological treatment recommendations from NICE guideline in people with cardiovascular conditions, regardless of the presence of hypertension.

1.1.4 Effectiveness evidence

1.1.4.1 Studies included in previous guideline versions

70 trials reported in 107 papers are summarised in this report.[1-9, 11-15, 17-34, 36-45, 47-57, 59-85, 87-90, 92-100, 102, 104-116] Study details are summarised in Table 15 to Table 35 in Appendix A.

The studies addressed the following comparisons:

Placebo comparisons

- Thiazide and thiazide-like diuretics versus placebo (9 trials)
- Beta-blocker versus placebo (5 trials)
- ACE inhibitor versus placebo (1 trial)
- Angiotensin-II receptor antagonist versus placebo (1 trial)
- Calcium channel blocker versus placebo (1 trial)

Head-to-head comparisons

- Calcium channel blocker versus ACE inhibitor (3 trials)
- Angiotensin-II receptor antagonist versus calcium channel blocker (1 trial)
- Angiotensin-II receptor antagonist versus thiazide-like diuretic (1 trial)
- ACE inhibitor versus thiazide or thiazide-like diuretic (3 trials)
- Calcium channel blocker versus thiazide or thiazide-like diuretic (8 trials)
- Beta blocker versus thiazide diuretic (3 trials)
- Angiotensin-II receptor antagonist versus beta blocker (1 trial)
- Calcium channel blocker versus beta blocker (3 trials)
- ACE inhibitor versus angiotensin-II receptor antagonist (3 trials)
- Diuretic versus diuretic (15 trials)
- Combination versus monotherapy (3 trials)

Second line therapy

- ACE inhibitor + calcium channel blocker versus ACE inhibitor + diuretic (1 trial)

Resistant hypertension

- Non-randomised evidence on spironolactone (6 trials)

Ethnicity

- ACE inhibitor versus other drug for angioedema (1 trial)

Age – younger (≤55 years)

- All drug classes compared with each other and placebo (3 studies)

Age – older (>80 years)

- Active versus placebo (1 meta analysis of 8 studies and 1 large RCT and its pilot trial).

Note that some studies covered more than 1 comparison and many were reported in more than one paper.

Data from the subset of studies with subgroup data for outcomes in those with and without CVD or in exclusively CVD populations are presented in evidence summaries, with further detail in the evidence tables (Appendix A), forest plots (Appendix B) and GRADE tables (Appendix C).

Details of the evidence from the remaining studies included in previous guideline versions can be found in NG136 and in the 2011, 2006 and 2004 versions.

1.1.4.2 Excluded studies

Studies cited in previous guidelines that did not present information relevant to this report are listed in the excluded studies list in Appendix E. NB as stated in Table 1 NG136 did not include people with cardiovascular disease and therefore were not considered further. These are not reflected in this excluded studies list.

1.1.5 Summary of effectiveness studies

In total, 41 studies (reported in 68 papers)[1, 3, 6-8, 11, 14-20, 22, 24, 26, 28, 30, 32, 37, 40, 42, 44-46, 48, 51-54, 56, 59-62, 64, 66, 70, 72, 75-82, 85, 88-90, 95, 97-100, 102, 104-113] included information on the proportion of people with CVD at baseline. In the majority of studies that reported details of the number of people with CVD at baseline, the subgroup comprised only a small proportion of the total study population.

Further analysis was undertaken for 6 studies that included only those with prior stroke or TIA[1, 32, 37, 64, 77, 105], 2 that included only those with pre-existing coronary artery disease,[78, 111, 112] and 6 that reported subgroup analyses for those with and without a history of cardiovascular disease.[26, 56, 78, 106, 112, 113] Details can be found in the evidence summaries below (Table 3 to Table 11).

Overview of studies: proportion of trial participants with CVD and available subgroup analyses

Table 2 summarises the populations and available subgroup analyses from all previously included studies.

Table 2: Overview of CVD evidence

Comparison	Trials reporting CVD at baseline (/total studies)	Proportion with CVD (available values as reported in studies)	Subgroup analysis findings	Comments
Placebo comparisons				
Thiazide and thiazide-like diuretics vs placebo	9/13 2 of which excluded established CVD[6, 32, 57, 72 7, 33, 39, 48, 70, 77, 79-81, 85, 89, 95, 106]	**Stroke/TIA**: 0%, 0%, 0.7%, 1%, 1.4%, 6.8%, 100%, 100% **MI**: 0%, 0%, 1.4%, 16%, 4.4%, 4.9%, 3.1%	**MRC and MRC-O**: Higher risk of stroke, coronary event, CV death and all-cause death in those with ischaemic vs non-ischaemic ECG changes (but this was not analysed according to treatment group). **SHEP**: Reported results with and without MI and stroke history. No differences in effect size between those with and without CVD history for CHD, HF or stroke outcomes. See Figure 4 to Figure 9.	HSCSG and PATS studies all had prior stroke/TIA – no consistent heterogeneity across outcomes with other studies
BB vs placebo	5/7 1 of which excluded established	**Stroke/TIA**: 0%, 0.7%, 100%, 100% **MI**: 1.4%, 16%, 9.8%	**MRC and MRC-O**: Higher risk of stroke, coronary event, CV death and all-cause death in those with ischaemic vs non-ischaemic ECG changes (but	

Comparison	Trials reporting CVD at baseline (/total studies)	Proportion with CVD (available values as reported in studies)	Subgroup analysis findings	Comments
	CVD[18, 21, 25, 37, 70, 72, 105]		this was not analysed according to treatment group)	
ACE-I vs placebo	1/1[64]	**Stroke/TIA**: 100% (only 48% hypertension)	Rates of stroke and major vascular events comparable among HT and non-HT	
ARB vs placebo	1/1[46, 62]	**Stroke**: 3.9% **MI**: 4.5%	-	
CCB vs placebo	1/1[3, 19, 40, 98-100]	**Stroke**: 4.1% **MI**: 11.6% **CHD**: 29.3% **Cerebrovascular disease**: 3.2%	Presence of CVD complications at baseline increase risk of mortality, fatal and non-fatal stroke or cardiac events.	No information on interaction with treatment.
Head-to-head comparisons				
CCB vs ACE-I	3/3 1 included all with CAD[24, 44, 45, 56, 59, 75, 76, 82, 111, 112]	**CHD**: 25%, 9,3% **Stroke**: 5.0% **MI/stroke**: 23% **Angina**: 65%, **MI**: 4.2%, 42% **Asymptomatic MI**: 12% **Coronary revascularisation**: 13% **Other CVD:** 5.6%, 23.8%	**ALLHAT**: no significant interactions between treatment (lisinopril vs amlodipine) and CHD history (yes vs no) for any outcomes reported in the study. However, see Figure 10 to Figure 15. **JMIC-B** (all had CAD): CCB favoured over ACE-I for reduced hospitalisation for angina in those with history of MI. This differed from those with no history of MI. See Figure 17 and Figure 18.	JMIC-B trial in which all had prior CAD – no heterogeneity with other studies
ARB vs CCB	1/1[52]	**Stroke or TIA:** 19.8% **CHD:** 45.6%, **PAD**: 13.8%,	-	-
ARB vs thiazide-like diuretics	1/1[66]	**Atherosclerotic CVD**: 45%	-	-
ACEI vs thiazide-like diuretics	2/3[75, 110, 115]	**MI or stroke**: 22.7% **Cerebrovascular disease:** 5% **Coronary revascularisation**: 13.5% **Other atherosclerotic CVD**: 23.8%	-	-

Comparison	Trials reporting CVD at baseline (/total studies)	Proportion with CVD (available values as reported in studies)	Subgroup analysis findings	Comments
		CHD: 8%, 25.3%		
CCB vs thiazide or thiazide-like diuretics	5/8 1 excluded CVD[11, 14, 15, 17, 54, 67, 75, 88, 93, 94, 104, 116]	**CHD**: 0%, 6%, 6.4% **Prior MI**: 0%, 1.9%, 6.1% **PVD:** 0%, 5.6% **Angina**: 0%, 0.7% **Coronary bypass**: 0%, 1.5% **Cardiac or cerebrovascular disease**: 0%, 5%, 51.4%	**INSIGHT**: Angina, PVD, MI, but not diabetes, predictors of outcome (composite of death from cardio or cerebrovascular cause, nonfatal stroke MI and heart failure) in unadjusted analysis on full study cohort (not randomised groups)	-
BB vs thiazide diuretics	3/3 1 excluded CVD[70, 72, 109]	**Stroke**: 0%, 0.7%; **MI**: 0%, 1.4%, 16%	**MRC and MRC-O**: Higher risk of stroke, coronary event, CV death and all-cause death in those with ischaemic vs non-ischaemic ECG changes (but this was not analysed according to treatment group)	-
ARB vs BB	1/1[22, 60, 61 30, 42, 90, 107, 108]	**Any vascular disease**: 25% **Coronary heart disease** 15.9%; **Cerebrovascular disease** 8%; **PVD**: 5.7%; **HF**: 1.8%	-	-
CCB vs BB	2/3 1 included only those with CAD[20, 26, 78, 114]	**Stroke/TIA**: 5%, 11% **MI**: 23%, 52.6% **Angina**: 66% **CABG or PCI**: 27.3% **PVD**: 5.5%, 6% **Other CVD**: 6%	**ASCOT**: No differences in relative effect of CCB vs BB for CV events and procedures with vs without prior vascular disease. See Figure 19. **INVEST** (all had CAD): No differences in relative effect of CCB vs BB for first event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) with vs without MI and with vs without revascularisation. But, for those with prior heart failure, BB favoured over CCB. See Figure 20, Figure 21 and Figure 22	-
ACE-I vs ARB	3/3[97, 102, 113]	**Stroke**: 0%, 21.0% **IHD**: 25.4%, **MI**: 0%, 11.7%, 49% **HF**: 5.7% **CAD**: 74.4%	**ONTARGET**: no interaction between prior CVD and incidence of primary outcome for ramipril vs telmisartan	-

Comparison	Trials reporting CVD at baseline (/total studies)	Proportion with CVD (available values as reported in studies)	Subgroup analysis findings	Comments
		Stable angina: 35% **Unstable angina**: 15% **CABG:** 22%		
Diuretic vs diuretic	2/15 1 excluded CVD, 1 only those with stroke/TIA (but not all had HT) [1, 9, 12, 13, 34, 36, 38, 41, 47, 49, 53, 83, 84, 87, 96]	**Stroke/TIA**: 0%, 100%	-	-
Combination vs monotherapy	0/3[4, 5, 23, 27, 63, 68, 71]	-	-	-
Second line therapy				
ACE-I + CCB vs ACE-I +diuretic	1/1[51]	**Stroke**: 13% **MI**: 23.5% **Unstable angina hospitalisation**: 11.5%, **Coronary revascularisation**: 36%	-	-
Resistant hypertension				
Non-randomised evidence on spironolactone	1/6[20, 28, 43, 55, 65, 92]	**CVD**: 57%	% with CVD similar across different response groups (SBP/DBP response ≤10% vs >10%)	-
Ethnicity subgroup				
ACE-I vs CCB vs diuretic vs ARB	0/1[56, 82]	**CVD**: 52% in full trial, not reported for black/non-black subgroups	-	-
Age: younger adults (≤55 years) subgroup				
Multiple comparisons including ACE-I, CCB, ARB, BB,	0/4[29, 31, 69]	-	-	-

Comparison	Trials reporting CVD at baseline (/total studies)	Proportion with CVD (available values as reported in studies)	Subgroup analysis findings	Comments
thiazide diuretic, and placebo				
Age: older adults (>80 years) subgroup				
Multiple comparisons including ACE-I, CCB, or BB vs placebo	3/3[7, 8, 16]	**Total CVD**: 12% **Stroke**: 4.0%, 4.5%, 6.8% **MI**: 3.0%, 3.1%, 5.0%	-	-

ACE-I: ACE inhibitor; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB: angiotensin II receptor blocker; ASCOT: the Anglo-Scandinavian Cardiac Outcomes Trial; BB: beta blocker; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCB: calcium channel blocker; CHD: coronary heart disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; HSCSG: Hypertension-Stroke Cooperative Study Group; IHD: ischaemic heart disease; INSIGHT: the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment; INVEST: The International Verapamil-Trandolapril Study; JMIC-B: Japan Multicenter Investigation for Cardiovascular Diseases-B; MI: myocardial infarction; MRC: Medical research council trial; MRC-O: Medical research council trial in older adults; ONTARGET: Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; SBP: systolic blood pressure; PAD: peripheral arterial disease; PATS: Post-stroke antihypertensive treatment study; PCI: percutaneous intervention; PVD: peripheral vascular disease; SHEP: Systolic Hypertension in the Elderly Program; TIA: transient ischaemic attack.

For further details of these studies please refer to Appendix A.1.

1.1.6 Summary of the effectiveness evidence for the CVD population

1.1.6.1 Subgroup analysis for those with and without CVD history

The evidence summaries in this section present data not previously analysed within the guideline evidence reports. These data inform whether the presence versus absence of specific cardiovascular disease history modifies the antihypertensive drug treatment effect for each comparison.

Thiazide-like diuretics versus placebo

Table 3: Clinical evidence summary: subgroups with and without history of MI or stroke for cardiovascular outcomes

Outcomes Follow up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (thiazide-like diuretic vs placebo) and CVD history (yes vs no)
					Risk with placebo	Risk difference with thiazide-like diuretic	
MI history							
Coronary heart disease 4.5 years	With MI history	229 (1 observational study)	⊕◯◯◯ VERY LOW a,b	RR 0.68 (0.25 to 1.86)	78 per 1,000	25 fewer per 1,000 (58 fewer to 67 more)	I^2 for interaction = 0% (p=0.58) No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of MI
	No MI history	4403 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.76 (0.58 to 0.98)	57 per 1,000	14 fewer per 1,000 (24 fewer to 1 fewer)	
Heart failure 4.5 years	With MI history	229 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.47 (0.19 to 1.20)	112 per 1,000	59 fewer per 1,000 (91 fewer to 22 more)	I^2 for interaction = 0% (p=0.75) No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of MI
	No MI history	4403 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.56 (0.40 to 0.78)	41 per 1,000	18 fewer per 1,000 (24 fewer to 9 fewer)	
Stroke 4.5 years	With MI history	229 (1 observational study)	⊕◯◯◯ VERY LOW a,b	RR 0.68 (0.20 to 2.36)	52 per 1,000	17 fewer per 1,000 (41 fewer to 70 more)	I^2 for interaction = 0% (p=0.92) No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of MI
	No MI history	4403 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.64 (0.50 to 0.82)	69 per 1,000	25 fewer per 1,000 (35 fewer to 12 fewer)	
Stroke history							
Coronary heart disease	With stroke history	65 (1	⊕◯◯◯ VERY LOW a,b	RR 1.71 (0.16 to 17.98)	33 per 1,000	24 more per 1,000 (28 fewer to 566 more)	I^2 for interaction = 0% (p=0.49)

Outcomes Follow up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (thiazide-like diuretic vs placebo) and CVD history (yes vs no)
					Risk with placebo	Risk difference with thiazide-like diuretic	
4.5 years		observational study)					No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of stroke
	No stroke history	4567 (1 observational study)	⨁◯◯◯ VERY LOW a,c	RR 0.74 (0.58 to 0.96)	58 per 1,000	15 fewer per 1,000 (24 fewer to 2 fewer)	
Heart failure 4.5 years	With stroke history	65 (1 observational study)	⨁◯◯◯ VERY LOW a,b	RR 0.29 (0.03 to 2.60)	100 per 1,000	71 fewer per 1,000 (97 fewer to 160 more)	I^2 for interaction = 0% (p=0.58) No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of stroke
	No stroke history	4567 (1 observational study)	⨁⨁◯◯ LOW a	RR 0.53 (0.39 to 0.74)	44 per 1,000	20 fewer per 1,000 (27 fewer to 11 fewer)	
Stroke 4.5 years	With stroke history	65 (1 observational study)	⨁◯◯◯ VERY LOW a,b	RR 0.69 (0.20 to 2.32)	167 per 1,000	52 fewer per 1,000 (133 fewer to 220 more)	I^2 for interaction = 0% (p=0.92) No evidence of interaction: similar degree of benefit of chlorthalidone in those with and without a history of stroke
	No stroke history	4567 (1 observational study)	⨁◯◯◯ VERY LOW a,c	RR 0.64 (0.50 to 0.82)	67 per 1,000	24 fewer per 1,000 (34 fewer to 12 fewer)	

a. High attrition bias (withdrawals) and high proportion of those in placebo group received active treatment. Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crossed both MIDs
c. 95% CI crosses one MID

Calcium channel blockers versus ACE inhibitors

Table 4: Clinical evidence summary: subgroups with and without history of coronary heart disease or MI for cardiovascular outcomes and mortality

Outcomes Follow up	Subgroup	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (calcium channel blocker vs ACE inhibitor) and CVD history (yes vs no)
					Risk with ACE inhibitor	Risk difference with calcium channel blocker	
Coronary heart disease history							
Mortality 4.9 years	With CHD history	4472 (1 observational study)	⨁◯◯◯ VERY LOW a,b	RR 0.88 (0.78 to 1.00)	184 per 1,000	22 fewer per 1,000 (41 fewer to 0 fewer)	I^2 for interaction = 52% (p=0.15) No evidence of significant interaction: trend for CCB being more favoured in those with a history of CHD
	No CHD history	13492 (1 observational study)	⨁◯◯◯ VERY LOW a,b	RR 0.99 (0.91 to 1.08)	131 per 1,000	1 fewer per 1,000 (12 fewer to 11 more)	
Coronary heart disease events 4.9 years	With CHD history	4472 (1 observational study)	⨁⨁◯◯ LOW a	RR 0.97 (0.83 to 1.13)	132 per 1,000	4 fewer per 1,000 (22 fewer to 17 more)	I^2 for interaction = 0% (p=0.62) No evidence of interaction: no clinical difference between CCB and ACE inhibitor in those both with and without a history of CHD
	No CHD history	13492 (1 observational study)	⨁⨁◯◯ LOW a	RR 1.02 (0.90 to 1.15)	74 per 1,000	1 more per 1,000 (7 fewer to 11 more)	
Stroke 4.9 years	With CHD history	4472 (1 observational study)	⨁◯◯◯ VERY LOW a,c	RR 0.78 (0.61 to 1.00)	61 per 1,000	13 fewer per 1,000 (24 fewer to 0 fewer)	I^2 for interaction = 0% (p=0.62) No evidence of interaction: no clinical difference between CCB and ACE inhibitor in those both with and without a history of CHD
	No CHD history	13492 (1 observational study)	⨁◯◯◯ VERY LOW a,c	RR 0.85 (0.72 to 0.99)	47 per 1,000	7 fewer per 1,000 (13 fewer to 0 fewer)	
Heart failure – 4.9 years	With CHD history	4472 (1	⨁◯◯◯ VERY LOW a,c	RR 1.12 (0.94 to 1.32)	102 per 1,000	12 more per 1,000 (6 fewer to 33 more)	I^2 for interaction = 0% (p=0.55)

Outcomes Follow up	Subgroup	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (calcium channel blocker vs ACE inhibitor) and CVD history (yes vs no)
					Risk with ACE inhibitor	Risk difference with calcium channel blocker	
		observational study)					No evidence of interaction: ACE inhibitor favoured in those both with and without a history of CHD (but no clinical difference)
	No CHD history	13492 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 1.19 (1.04 to 1.36)	56 per 1,000	11 more per 1,000 (2 more to 20 more)	
Angina (hospitalised or treated) – 4.9 years	With CHD history	4472 (1 observational study)	⊕⊕◯◯ LOW a	RR 1.03 (0.92 to 1.15)	207 per 1,000	6 more per 1,000 (17 fewer to 31 more)	I^2 for interaction = 73.1% (p=0.05) Evidence of interaction: CCB favoured in those without a history of CHD but not in those with a history of CHD (but no clinical difference between CCB and ACE inhibitor in either subgroup)
	No CHD history	13492 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.87 (0.78 to 0.98)	80 per 1,000	10 fewer per 1,000 (18 fewer to 2 fewer)	
Coronary revascularisation – 4.9 years	With CHD history	4472 (1 observational study)	⊕⊕◯◯ LOW a	RR 1.00 (0.86 to 1.15)	141 per 1,000	0 fewer per 1,000 (20 fewer to 21 more)	I^2 for interaction = 0% (p=0.73) No evidence of interaction: no clinical difference between CCB and ACE inhibitor in those both with and without a history of CHD
	No CHD history	13492 (1 observational study)	⊕⊕◯◯ LOW a	RR 1.03 (0.90 to 1.18)	59 per 1,000	2 more per 1,000 (6 fewer to 11 more)	
Peripheral arterial disease – 4.9 years	With CHD history	4472 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 1.10 (0.85 to 1.43)	45 per 1,000	4 more per 1,000 (7 fewer to 19 more)	I^2 for interaction = 82.5% (p=0.02) Evidence of interaction: CCB favoured in those without a history of CHD but not in those with a history of CHD (but no clinical difference between CCB and ACE inhibitor in either subgroup)
	No CHD history	13492 (1 observational study)	⊕◯◯◯ VERY LOW a,c	RR 0.73 (0.60 to 0.90)	31 per 1,000	8 fewer per 1,000 (12 fewer to 3 fewer)	
Myocardial infarction history							

Outcomes Follow up	Subgroup	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (calcium channel blocker vs ACE inhibitor) and CVD history (yes vs no)
					Risk with ACE inhibitor	Risk difference with calcium channel blocker	
Cardiac events – 3 years	With MI history	696 (1 observational study)	⨁◯◯◯ VERY LOW d,e	HR 0.91 (0.63 to 1.31)	Not estimable	-	I^2 for interaction = 28.7% (p=0.24) No evidence of interaction: trend towards ACE inhibitor being less favoured in those with a history of MI
	No MI history	954 (1 observational study)	⨁◯◯◯ VERY LOW c,d	HR 1.26 (0.85 to 1.87)	Not estimable	-	
Hospitalisation for angina 3 years	With MI history	696 (1 observational study)	⨁⨁◯◯ LOW c,d	HR 0.42 (0.22 to 0.80)	Not estimable	-	I^2 for interaction = 85.6% (p=0.008) Evidence of interaction: CCB more favoured in those with a history of MI
	No MI history	954 (1 observational study)	⨁◯◯◯ VERY LOW d,e	HR 1.29 (0.76 to 2.19)	Not estimable	-	

a. High attrition bias (withdrawals greater than event rate). Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crosses the line of no effect
c. 95% CI crosses one MID
d. High attrition bias (withdrawals similar to or greater than event rate). Post-hoc subgroup analysis of RCT adjusted for sex, age, history of myocardial infarction and angina pectoris, but unclear how outcomes were selected.
e. 95% CI crosses both MID

Calcium channel blockers versus beta blockers

Table 5: Clinical evidence summary: subgroups with and without history of vascular disease, myocardial infarction, heart failure or revascularisation for cardiovascular outcomes and mortality

Outcomes Follow-up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (calcium channel blocker vs beta blocker) and CVD history (yes vs no)
					Risk with beta blocker	Risk difference with calcium channel blocker	
Vascular disease history							
Cardiovascular events and procedures median 5.5 years	With prior vascular disease	3147 (1 observational study)	⨁⨁◯◯ LOW a,b	HR 0.80 (0.70 to 0.91)	280 per 1,000	49 fewer per 1,000 (75 fewer to 22 fewer)	I^2 for interaction = 0% (p=0.45) No evidence of interaction: similar degree of benefit of CCB in those with and without a history of vascular disease
	No prior vascular disease	16629 (1 observational study)	⨁⨁◯◯ LOW a,b	HR 0.85 (0.78 to 0.93)	140 per 1,000	20 fewer per 1,000 (29 fewer to 9 fewer)	
Myocardial infarction (MI) history							
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) mean 2.7 years	With MI history	7218 (1 observational study)	⨁⨁⨁◯ MODERATE a	RR 0.95 (0.85 to 1.07)	144 per 1,000	7 fewer per 1,000 (22 fewer to 10 more)	I^2 for interaction = 0% (p=0.57) No evidence of interaction: no clinical difference between CCB and BB in those both with and without a history of MI
	No MI history	15358 (1 observational study)	⨁⨁⨁◯ MODERATE a	RR 0.99 (0.89 to 1.11)	82 per 1,000	1 fewer per 1,000 (9 fewer to 9 more)	
Heart failure history							
First event (death, nonfatal MI, nonfatal	With heart failure history	1256 (1 observational study)	⨁⨁◯◯ LOW a,b	RR 1.21 (0.99 to 1.47)	218 per 1,000	46 more per 1,000 (2 fewer to 103 more)	I^2 for interaction = 79% (p=0.03)

Outcomes Follow-up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (calcium channel blocker vs beta blocker) and CVD history (yes vs no)
					Risk with beta blocker	Risk difference with calcium channel blocker	
stroke, CV death, CV hospitalisation) – mean 2.7 years	No heart failure history	21320 (1 observational study)	⨁⨁⨁◯ MODERATE a	RR 0.95 (0.87 to 1.03)	95 per 1,000	5 fewer per 1,000 (12 fewer to 3 more)	Evidence of interaction: benefit of BB greater in those with a history of heart failure (no clinical difference in those without heart failure history).
Revascularisation history							
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - mean 2.7 years	With revascularisation history	6166 (1 observational study)	⨁⨁⨁◯ MODERATE a	RR 0.96 (0.85 to 1.09)	145 per 1,000	6 fewer per 1,000 (22 fewer to 13 more)	I^2 for interaction = 0% (p=0.73) No evidence of interaction: no clinical difference between CCB and BB in those both with and without a history of revascularisation
	No revascularisation history	16410 (1 observational study)	⨁⨁⨁◯ MODERATE a	RR 0.99 (0.89 to 1.09)	85 per 1,000	1 fewer per 1,000 (9 fewer to 8 more)	

a. Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crosses one MID

ACE inhibitors versus angiotensin-II receptor blockers

Table 6: Clinical evidence summary: subgroups with and without history of CVD for composite outcome

Outcomes Follow-up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (ACE inhibitor vs ARB) and CVD history (yes vs no)
					Risk with ACE inhibitor	Risk difference with ARB	
Cardiovascular disease (CVD) history							
Death from cardiovascu	With CVD history	15,672 (1	⨁⨁◯◯ LOW a,b	Not reported	16.8%	-	p for interaction =0.79

Outcomes Follow-up	Subgroup	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interaction between treatment (ACE inhibitor vs ARB) and CVD history (yes vs no)
					Risk with ACE inhibitor	Risk difference with ARB	
lar causes, myocardial infarction, stroke, or hospitalisation for heart failure		observational study)					No evidence of interaction
	No CVD history	1486 (1 observational study)	⨁⨁◯◯ LOW a,b	Not reported	13.1%	-	

a. Pre-specified subgroup analysis of RCT with insufficient reporting.
b. Imprecision could not be assessed

1.1.6.2 Comparative treatment effects in adults with history of stroke or TIA

The evidence summaries in this section re-present data from studies with inclusion criteria limited to those with stroke and/or TIA. These studies were previously meta-analysed with studies in non-CVD populations within the guideline.

Table 7: Clinical evidence summary: thiazide-like diuretic vs placebo in adults with a history of prior stroke or TIA

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with thiazide-like diuretic
All-cause mortality	6103 (2 RCTs) 2 years	⊕⊕◯◯ LOW a,b,c	RR 0.94 (0.76 to 1.14)	60 per 1,000	4 fewer per 1,000 (14 fewer to 8 more)
Coronary heart disease (myocardial infarction, or sudden death)	6103 (2 RCTs) 2 years	⊕◯◯◯ VERY LOW a,b,d	RR 1.06 (0.63 to 1.77)	9 per 1,000	1 more per 1,000 (3 fewer to 7 more)
Stroke recurrence	6103 (2 RCTs) 2 years	⊕⊕◯◯ LOW a,b,e	RR 0.75 (0.63 to 0.89)	85 per 1,000	21 fewer per 1,000 (32 fewer to 9 fewer)
Total cardiovascular events	6103 (2 RCTs) 2 years	⊕⊕◯◯ LOW a,b,e	RR 0.77 (0.65 to 0.92)	88 per 1,000	20 fewer per 1,000 (31 fewer to 7 fewer)

a. Majority of the evidence at high risk of selection bias (unclear randomisation method and inadequate allocation concealment).
b. Note: Not all participants in PATS trial had diagnosed hypertension (16% <140/90 mmHg)
c. 95% CI crosses the line of no effect
d. 95% CI crosses both MIDs
e. 95% CI crosses one MID

Table 8: Clinical evidence summary: beta blocker versus placebo in adults with a history of stroke or TIA

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blocker
All-cause mortality	2193 (2 RCTs) 2.3-2.7 years	⊕⊕◯◯ LOW a,b,c	RR 0.95 (0.75 to 1.21)	108 per 1,000	5 fewer per 1,000 (27 fewer to 23 more)
Coronary heart disease events (cardiac death/non-fatal MI)	2193 (2 RCTs) 2.3-2.7 years	⊕◯◯◯ VERY LOW d,e,f	RR 1.01 (0.73 to 1.39)	63 per 1,000	1 more per 1,000 (17 fewer to 25 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blocker
Fatal or non-fatal stroke	2193 (2 RCTs) 2.3-2.7 years	⨁⨁◯◯ LOW a,b,g	RR 0.93 (0.74 to 1.17)	120 per 1,000	8 fewer per 1,000 (31 fewer to 20 more)

a. High risk of selection bias (1 study unclear and 1 study inadequate allocation concealment).
b. Note: only 29% of Dutch TIA trial had hypertension
c. 95% CI crosses the line of no effect
d. Majority of the evidence at high risk of attrition bias because >40% withdrew from the Dutch TIA study
e. Only 29% of Dutch TIA trial had hypertension
f. 95% CI crosses both MIDs
g. 95% CI crosses 1 MID

Table 9: Clinical evidence summary: ACE inhibitor versus placebo in adults with a history of stroke or TIA

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitor
All-cause mortality	6102 (1 RCT) 3.9 years	⨁◯◯◯ VERY LOW a,b,c	RR 0.96 (0.83 to 1.11)	104 per 1,000	4 fewer per 1,000 (18 fewer to 11 more)
Coronry heart disease events (non-fatal MI or death from coronary heart disease)	6102 (1 RCT) 3.9 years	⨁◯◯◯ VERY LOW a,b,d	RR 0.75 (0.59 to 0.95)	50 per 1,000	13 fewer per 1,000 (21 fewer to 3 fewer)
Fatal and non-fatal stroke	6102 (1 RCT) 3.9 years	⨁◯◯◯ VERY LOW a,b,d	RR 0.73 (0.64 to 0.84)	138 per 1,000	37 fewer per 1,000 (50 fewer to 22 fewer)
Total major vascular events (vascular death, non-fatal MI, non-fatal stroke)	6102 (1 RCT) 3.9 years	⨁◯◯◯ VERY LOW a,b,d	RR 0.76 (0.68 to 0.85)	198 per 1,000	47 fewer per 1,000 (63 fewer to 30 fewer)

a. High risk of attrition bias (>30% of participants withdrew from the trial)
b. Population indirectness: only 48% had hypertension
c. 95% CI crosses the line of no effect
d. 95% CI crosses one MID

1.1.6.3 Comparative treatment effects in adults with history of coronary artery disease

The evidence summaries in this section re-present data from studies with inclusion criteria limited to those with coronary artery disease. These studies were previously meta-analysed with studies in non-CVD populations within the guideline.

Table 10: Clinical evidence summary: calcium channel blocker versus ACE inhibitor in adults with a history of CAD

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ACE inhibitor	Risk difference with calcium channel blocker
All-cause mortality	1650 (1 RCT) 3 years	⊕⊕◯◯ LOW a,b	RR 0.79 (0.37 to 1.69)	18 per 1,000	4 fewer per 1,000 (11 fewer to 13 more)
Myocardial infarction	1650 (1 RCT) 3 years	⊕◯◯◯ VERY LOW a,c	RR 1.22 (0.59 to 2.52)	16 per 1,000	3 more per 1,000 (6 fewer to 24 more)
Stroke	1650 (1 RCT) 3 years	⊕◯◯◯ VERY LOW a,c	RR 0.99 (0.50 to 1.97)	19 per 1,000	0 fewer per 1,000 (10 fewer to 19 more)
Total cardiac events (cardiac death or sudden death; MI; angina requiring hospitalization; heart failure requiring hospitalization; serious arrhythmia or of coronary interventions)	1650 (1 RCT) 3 years	⊕⊕◯◯ LOW d,e	RR 1.09 (0.85 to 1.39)	129 per 1,000	12 more per 1,000 (19 fewer to 50 more)
Heart failure requiring hospitalisation	1650 (1 RCT) 3 years	⊕◯◯◯ VERY LOW a,c	RR 1.32 (0.56 to 3.12)	11 per 1,000	4 more per 1,000 (5 fewer to 23 more)
Angina requiring hospitalisation	1650 (1 RCT) 3 years	⊕◯◯◯ VERY LOW a,c	RR 0.89 (0.61 to 1.28)	68 per 1,000	7 fewer per 1,000 (27 fewer to 19 more)

a. Risk of attrition bias because rate of missing data is greater than the number of events.
b. 95% CI crosses the line of no effect
c. 95% CI crosses both MIDs
d. Risk of attrition bias because the level of missing data is comparable with the number of events.
e. 95% CI crosses one MID

Table 11: Clinical evidence summary: calcium channel blocker versus beta blocker in adults with a history of CAD

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with beta blocker	Risk difference with calcium channel blocker
All-cause mortality	22008 (1 RCT) 2.7 years	⊕⊕⊕◯ MODERATE a	RR 0.98 (0.90 to 1.08)	81 per 1,000	2 fewer per 1,000 (8 fewer to 6 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with beta blocker	Risk difference with calcium channel blocker
Non-fatal myocardial infarction	22008 (1 RCT) 2.7 years	⨁⨁⨁◯ MODERATE b	RR 0.99 (0.79 to 1.24)	14 per 1,000	0 fewer per 1,000 (3 fewer to 3 more)
Non-fatal stroke	22008 (1 RCT) 2.7 years	⨁⨁⨁◯ MODERATE b	RR 0.89 (0.71 to 1.13)	13 per 1,000	1 fewer per 1,000 (4 fewer to 2 more)

a. 95% CI crosses the line of no effect
b. 95% CI crosses one MID

1.1.7 Economic evidence

1.1.7.1 Studies included in previous guideline versions

One published health economic study was included for the 2011 review question about antihypertensives in older adults.[101]

No published health economic studies were included for other review questions in previous iterations of the guideline.

A cost-effectiveness model of first-line antihypertensive treatment in people without pre-existing CVD, heart failure or diabetes was also developed as part of CG34 (2006 update), and updated as part of CG127 (2011 update) (2011 full guideline report: Section 10.4, p228 & Appendix I p404).

These studies are summarised in Table 12 along with information about established CVD.

Table 12: Studies included economic analyses and established CVD

Included analysis	Comparators	Population	Established CVD	Notes
Szucs 2010[101] (HYVET RCT)	1. No treatment 2. Treatment	People aged over 80 years with hypertension	• HYVET: 12% of the study population had a history of CVD • No subgroup analysis for people with/without CVD	Although included for the CG127 review question about the most clinically and cost effective anti-hypertensive in people ages 80 years and older no separate recommendations were made about choice of antihypertensives in older people.
CG34 (2006)/CG 127 (2011) guideline model	First-line antihypertensive treatment: 1.No treatment 2.Thiazide-type diuretics 3.Beta blockers 4.ACE-I/ARB	People with hypertension excluding those with pre-existing cardiovascular disease (CVD), heart	• Model population excludes CVD • Baseline risks of model events were for people without CVD • Relative treatment effects of drugs were	Clinical events modelled were CVD events (non-fatal unstable angina, MI, heart failure and stroke) and CVD-related deaths. Adverse effects modelled were onset of heart failure and diabetes.

Included analysis	Comparators	Population	Established CVD	Notes
	5.CCB	failure (HF) or diabetes. Results stratified by age (>55 years), CVD risk, diabetes risk and heart failure risk.	based on 2006 systematic review of head-to-head studies and meta analysis which may include studies where people had CVD	Model developed as part of CG34 (2006). Limited update in CG127 (2011) of costs and relative risks for ARBs based on new ACE-I vs ARB data.

Abbreviations: ACE-I = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; CCB = calcium channel blockers; CG = NICE clinical guideline; CVD = cardiovascular disease; MI = myocardial infarction; RCT = randomised clinical trial.

CG34 (2006)/CG127 (2011) guideline model

The model developed to look at first line antihypertensive treatment in the 2006 guideline (with limited update in 2011) does not aim to assess cost-effectiveness of antihypertensive drugs in people with hypertension and established CVD. Baseline risk of CVD events is likely to be higher and AE risks (heart failure and diabetes) could also be different in a population with CVD. There may also be additional considerations for an established CVD population that aren't reflected appropriately by this analysis (e.g. the exclusion of people with diabetes and heart failure in the population may not be reasonable in an established CVD population and this could affect the model). However, some key results from the analysis are presented below with discussion about how generalisable these might be to a CVD population. Full model methods and results are available from the 2011 full guideline report: Section 10.4, p228 (summary and discussion) & Appendix I p404 (full technical report).

This analysis found that treating hypertension is highly cost-effective. Treatment resulted in improved health outcomes (higher QALYs) with all of the drug classes in the model and actually resulted in overall cost savings compared to no treatment as the reduction in cardiovascular events led to savings that offset the relatively low cost of antihypertensive medication; although it should be noted that this is based on low cost generic drugs. In most people CCBs were found to be the most cost-effective treatment option for initial treatment of essential hypertension in people without CVD, diabetes or heart failure. This is illustrated in Table 13 reproduced from the model report. The base case results are presented for 65-year-old men and women with an annual CVD risk of 2%, HF risk of 1% and diabetes risk of 1.1%. People with CVD will generally have a higher baseline risk of cardiovascular events and so if relative treatment effects remain the same (as in people with hypertension without CVD) there will be a greater number of CVD events avoided (additional cost savings and health benefits). CCBs were the most cost effective treatment option in the base case analysis.

Table 13: Base case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% HF risk)

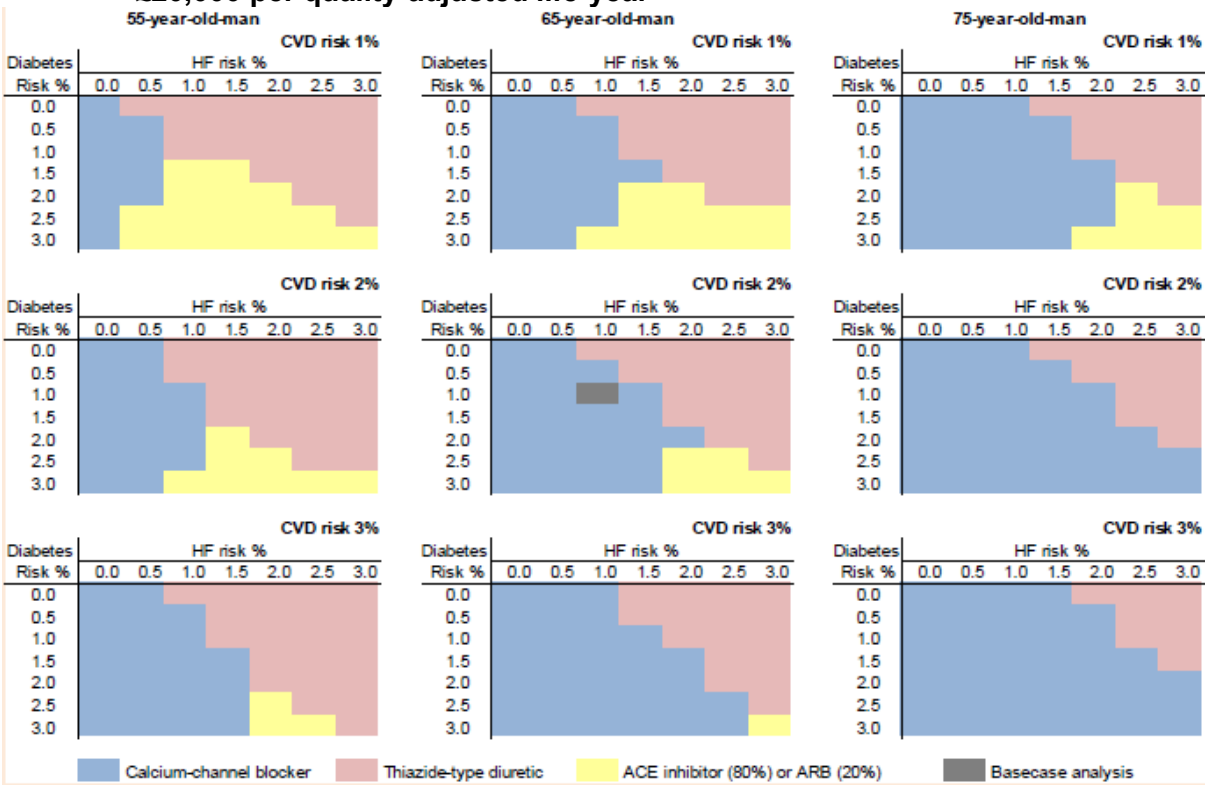
Men			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£3,910	10.22	LC
A	£4,010	10.21	-
C	£4,030	10.28	£1,960
B	£4,550	9.89	-
NI	£4,690	9.57	-
Women			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,310	10.65	LC
C	£4,390	10.71	£1,520
A	£4,400	10.63	-
B	£5,050	10.29	-
NI	£5,230	9.96	-

Source: Reproduced from the 2011 full guideline report: Section 10.4, p228 & Appendix I p404

Abbreviations: - = ruled out by dominance or extended dominance; A = ACE-I/ARB; B = beta blockers; C = CCBs; D = thiazide-type diuretics; ICER = incremental cost-effectiveness analysis (compared to next least costly once options ruled out by dominance or extended dominance have been excluded); LC = lowest cost; NI = no intervention; QALY = quality-adjusted life-year.

The most cost-effective antihypertensive treatment depended on baseline CVD risk, heart failure risk and diabetes risk. The CG127 committee concluded that CCBs were the most cost effective option in most people (over 55 years age) and this contributed to the recommendation for CCBs as a first line treatment option for people over 55 years. This is illustrated in Figure 1 and Figure 2 reproduced from the model report. CCBs were increasingly cost effective with increasing CVD risk. People with CVD will generally have higher risk of CVD events.

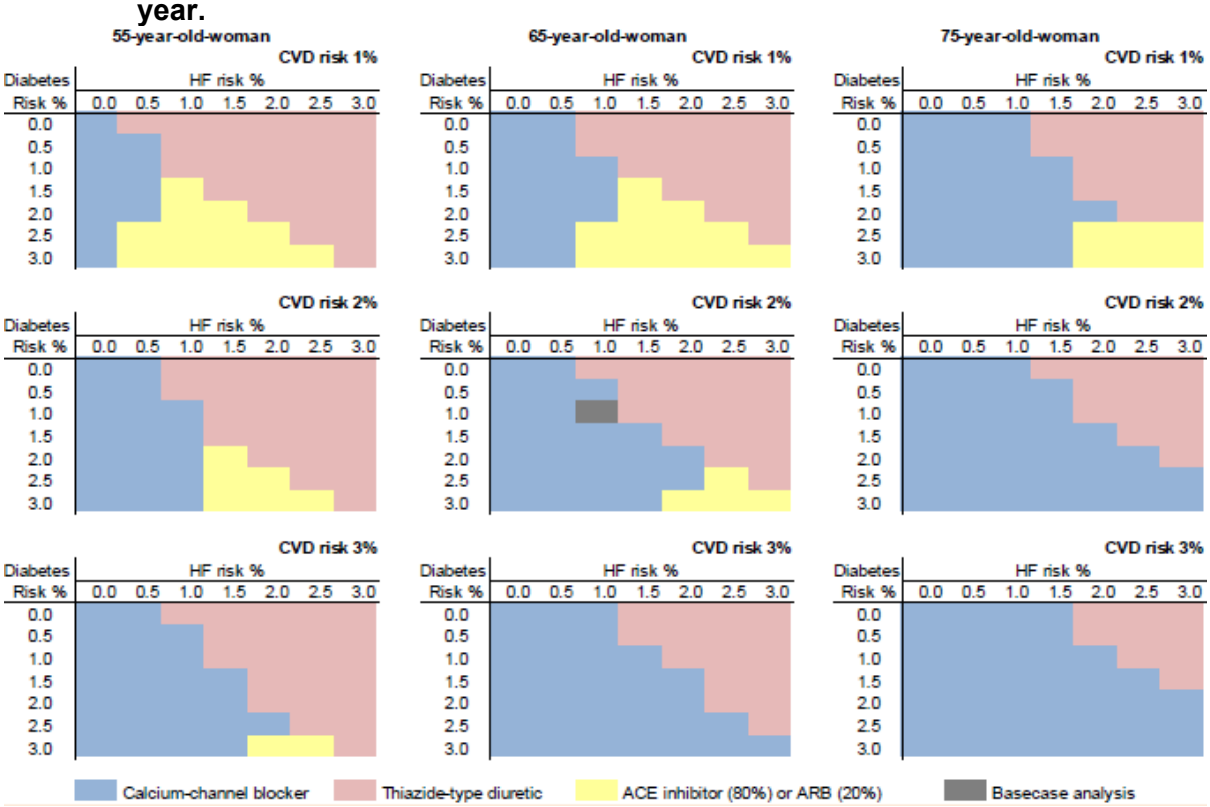
Figure 1: Four-way sensitivity analysis: most cost-effective (represented by colour) first-line drug for men by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year



Source: Reproduced from the 2011 full guideline report: Section 10.4, p228 & Appendix I p404

Abbreviations: HF = heart failure; CVD = cardiovascular disease.

Figure 2: Four-way sensitivity analysis: most cost-effective first-line drug for women by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year.

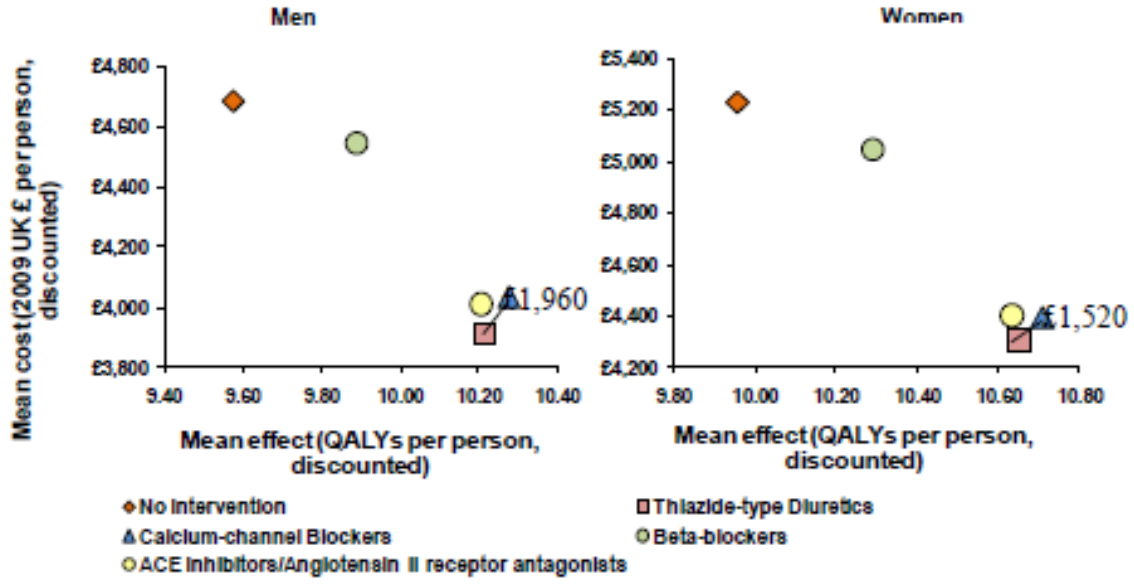


Source: Reproduced from the 2011 full guideline report: Section 10.4, p228 & Appendix I p404

Abbreviations: HF = heart failure; CVD = cardiovascular disease.

Total costs and QALYs were similar between CCBs, ACE-I/ARBs and thiazide-like diuretics in the analysis. This is illustated in Table 13 and Figure 3 below reproduced from the model report. Therefore, if relative treatment effects vary between people with established CVD and without, conclusions may be sensitive to this.

Figure 3: 2011 base-case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% heart failure risk)



Source: Reproduced from the 2011 full guideline report: Section 10.4, p228 & Appendix I p404

Abbreviations: QALY = quality-adjusted life-year.

1.1.8 Economic model

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

1.1.9 Unit costs

Different classes of antihypertensive may be associated with different costs. Some illustrative current unit costs of antihypertensive drugs are provided below. Usual daily dose is based on BNF dosing information for hypertension.

Table 14: Antihypertensive drug costs

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

Drug	Usual daily dose	Cost per year
Nifedipine	Depends on formulation (MR)	£47 to £350
Verapamil hydrochloride	240-480mg (IR and MR formulations)	£39 to £617
Diuretics		
Chlortalidone	25-50mg	£536 to £1071
Indapamide	2.5mg / MR 1.5mg	£24 to £41
Xipamide	20mg	£51

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

Source: BNF 19th July 2021.[10] Usual daily dose based on dosing information for hypertension indication. Drug tariff costs (as listed in BNF) used in costing.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

Outcomes were taken from previously published versions of the NICE guideline on hypertension in adults.

This included the following outcomes, where available, according to the year of guideline publication:

2004

- All-cause mortality
- Coronary heart disease events
- Cerebrovascular events
- Cardiovascular events

2006

- Mortality from any cause
- Stroke (ischaemic or haemorrhagic)
- Myocardial infarction (including, where reported, silent MI)
- Heart failure
- New-onset diabetes mellitus
- Vascular procedures (including both coronary and carotid artery procedures)
- Incidence of unstable angina (or angina episodes requiring hospitalisation)

2011

- Effectiveness
- Mortality from any cause
- Stroke (ischaemic or haemorrhagic)
- Myocardial infarction (MI) (including, where reported, silent MI)
- Heart failure
- New onset diabetes
- Vascular procedures (including both coronary and carotid artery procedures)
- Angina requiring hospitalisation
- Health-related quality of life (to use what is reported by trials)

- Major adverse cardiac and cerebrovascular events (MAACE): fatal and non-fatal MI, fatal non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation (and different composites of this outcome)
- Angioedema in black people of African and Caribbean descent

2019

- All-cause mortality
- Health-related quality of life
- Stroke (ischaemic or haemorrhagic)
- Myocardial infarction (MI)
- Heart failure needing hospitalisation
- Vascular procedures (including both coronary and carotid artery procedures)
- Angina needing hospitalisation
- Discontinuation or dose reduction due to side effects
- Side effect 1: Acute kidney injury
- Side effect 2: New onset diabetes
- Side effect 3: Changes in 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]

The outcome of withdrawal from treatment from the 2004, 2006 and 2011 versions of the guideline was not included in the outcome analysis because it was not originally meta-analysed owing to potential variability or subjectivity of recording. Therefore, this has been included as narrative information in the study summaries only. Similarly, from the 2004 guideline, the data on blood pressure achieved, percentage on monotherapy at the end of the trial and percentage achieving the target blood pressure were not subject to meta-analysis in this report because they were not analysed originally and do not represent clinical end-points that would be informative for recommendations.

1.1.10.2 The quality of the evidence

Two different types of evidence were assessed in this report (pertaining to studies published up to November 2010).

1. **Evidence from subgroup analyses of RCTs** was sought to assess whether there was a difference in the effect estimates for anti-hypertensive drugs between those with and without established cardiovascular disease (CVD).
   These subgroup analyses were almost all post-hoc and lacked any adjustment for potential confounding in the non-randomised comparisons. Additionally, the subgroup with CVD was usually a minority of the total study sample, resulting in small numbers of events and uncertainty in the estimates. This reduced confidence in the findings when comparing the absolute risk difference between the subgroups. The majority of this evidence was of low or very low quality. The exception to this was in the comparison of calcium channel blockers with beta blockers relating to history of MI, heart failure or revascularisation, which was of moderate quality. This supported the overall findings from the whole body of evidence that there was no conclusive evidence of any requirement for different drugs to be considered in people with established CVD.
2. **Evidence from RCTs in CVD populations** that inform the efficacy of different drugs specifically in people with established CVD.
   There were 5 studies that reported clinical endpoints in adults with a history of stroke

or TIA, covering only a minority of relevant comparisons, and importantly not including evidence on calcium channel blockers. This evidence ranged from low to very low quality and was insufficient in quality and quantity to support any change in recommendations.
There were 2 studies in adults with a history of coronary artery disease. Evidence from 1 small study for the comparison of calcium channel blocker versus ACE inhibitor was of low to very low quality, while evidence for the comparison of calcium channel blocker versus beta blocker from a larger study was of moderate quality. This evidence was insufficient in scope and quality to inform any specific recommendation about anti-hypertensive drug choice in people with a history of coronary heart disease, but also did not suggest that different treatment is required for this group. Research recommendations have not been made as a full systematic review and search were not conducted.

1.1.10.3 Benefits and harms

Subgroup analysis comparing those with and without established CVD

The majority of the evidence across all available comparisons and for all reported CVD diagnoses did not demonstrate any clear or consistent clinically important difference in the effectiveness of anti-hypertensive drugs between those with and without a history of CVD. There was a trend towards a greater absolute benefit of thiazide diuretics compared with placebo for reduced risk of coronary heart disease, heart failure or stroke outcomes in those with a history of MI compared to those without and those with a history of stroke compared to those without. However, the difference was not clinically important and the committee did not have confidence in the findings based on a subgroup analysis from a single study. Similarly, the absolute benefit of calcium channel blockers compared with ACE inhibitors for reduced risk of all-cause mortality was greater in those with a history of coronary heart disease than in those without. However, this evidence from a single study was insufficient in scope and quality to support a change in recommendations. Finally, there was a greater benefit of beta blockers compared with calcium channel blockers for the outcome of first event (death, non-fatal MI, non-fatal stroke, CV death, CV hospitalisation) in those with a history of heart failure. The committee noted that this supports the existing recommendation that people with chronic heart failure should be offered a beta blocker and an ACE inhibitor.

A statistically significant interaction between treatment and CV history was rarely identified and on review of these data the committee determined that there was either no clinically significant difference in the outcomes between the subgroups or that it could not be adequately assessed.

Studies in those with a history of stroke or TIA

The committee noted that only comparisons with placebo were available in these studies. Only small differences in absolute risk were seen between thiazide or thiazide-like diuretics, beta blockers and ACE inhibitors compared with placebo in this population across all outcomes. The committee noted the borderline clinically significant benefit of thiazide or thiazide-like diuretics for reduced stroke recurrence and total cardiovascular events. However, there was insufficient evidence to recommend thiazide-like diuretics as the first choice in those with a history of stroke owing to the small absolute benefit and the absence of evidence for any active comparisons.

Studies in those with a history of coronary artery disease

No clinically important differences were found for the comparison of calcium channel blockers with either ACE inhibitors or beta blockers for this population, although a small reduction in the risk of mortality was seen with calcium channel blockers compared to ACE inhibitors (4 fewer per 1000) or beta blockers (2 fewer per 1000). This evidence did not justify any change to the standard treatment algorithm in this subgroup.

Conclusions from the evidence

Overall, the evidence assessed, which was limited to studies previously included in the hypertension guideline, did not support any deviation from the existing hypertension treatment algorithm for people with established CVD. Importantly, evidence from the subgroup analyses consistently failed to demonstrate any clinically relevant difference in outcomes between those with and without a history of CVD. It was noted by the committee that studies in those with a history of stroke/TIA or coronary artery disease were limited in number and did not cover enough treatment comparisons to draw any firm conclusions. Therefore, in terms of anti-hypertensive drug therapy, no specific new recommendations were made for those with a history of CVD and all existing recommendation should apply including considerations for age and ethnicity. There are already clear recommendations on pharmacological management for those with MI, angina and heart failure in the relevant NICE guidelines. Such recommendations are currently lacking for those who have had strokes or TIAs.

Considerations from other NICE guidelines and clinical experience

The committee noted that the NICE acute coronary syndromes guideline (NG185) published in 2020 includes recommendations that all people that have had an MI should receive an ACE or ARB and a beta blocker as part of secondary prevention. It is also recommended that people should not routinely be offered a CCB post-MI but recommendations note that they may be used to treat hypertension once their condition is subsequently stable. The committee agreed that disease-specific secondary prevention recommendations for people with MI should be applied first and for people that remain hypertensive the existing recommendations in this guideline on hypertension should be used to guide addition of further anti-hypertensive drugs.

The committee also noted that, unlike for ACS, there are currently no recommendations relating to use of any of the anti-hypertensive drug classes for secondary prevention in NICE stroke-specific guidelines. In the hypertension guideline reviews, studies in people who have had a stroke/TIA have sometimes been included whether or not the population is also hypertensive. Three out of the 6 studies in populations with prior stroke or TIA were not exclusively in hypertensive individuals (the DUTCH-TIA, PATS, and PROGRESS studies). The committee highlighted a perceived preference for stroke physicians to initiate ACE inhibitor + indapamide in patients who have had a stroke or TIA (with and without hypertension) – a decision based on the results of the PROGRESS and PATS studies. The PROGRESS study randomised patients to perindopril or no treatment, with indapamide added to perindopril at the clinician's discretion (i.e. not randomised). The committee highlighted that a post-hoc analysis showed a reduction in future stroke risk only in the combined perindopril + indapamide group and not in those treated with perindopril alone. This was independent of a prior diagnosis of hypertension. The PROGRESS study was included in the 2004 hypertension guideline review but the non-randomised subgroup analysis was not and so this evidence was not considered by the committee on this occasion. Further discussions centred around the merits of other anti-hypertensive drug classes in people who have experienced stroke/TIA, but despite some difference of opinion between committee members general agreement concerning the following points was achieved:

1. The importance of achieving blood pressure control in patients following stroke/TIA was paramount.
2. Variation in efficacy between drug classes in patients following stroke/TIA could not be robustly or consistently identified given the data available up to November 2010.
3. A scientific / mechanistic explanation as to why 1 particular anti-hypertensive drug or drug class might produce a greater effect on future CVD risk is not currently known.
4. The existing hypertension treatment algorithm appears to be broadly embedded in routine clinical practice and is simple to follow – this could be undermined by

introducing condition-specific recommendations which are not supported by consistent, robust data.

Taking into account these considerations, the committee agreed that the evidence was not currently sufficient to warrant any specific recommendations in terms of anti-hypertensive drug therapy for people who are hypertensive and have suffered a stroke or TIA (or any form of CVD). Therefore, the committee recommended that anti-hypertensive drug treatment should be offered to people with cardiovascular disease in line with the existing recommendations if they remain hypertensive after disease-specific management options have been implemented.

1.1.10.4 Cost effectiveness and resource use

Two economic evaluations related to anti-hypertensive drugs were identified from previously published versions of the NICE guideline on hypertension in adults: 1 published economic evaluation and 1 original economic model.

The published economic evaluation compared treatment versus no treatment for people over 80 years of age with hypertension based on the HYVET study. In this study 12% of people had a history of CVD. The economic evaluation did not undertake any subgroup analysis for people with and without CVD.

The original economic evaluation compared different classes of first-line anti-hypertensive and no treatment in people over 55 years with hypertension excluding those with pre-existing cardiovascular disease, heart failure or diabetes. It was developed as part of CG34 (2006) with a limited update in CG127 (2011). This model did not aim to assess cost effectiveness in a CVD population, however, given it informed the guideline recommendations about anti-hypertensive drugs, the committee considered whether there was reason to believe cost-effectiveness conclusions might be different in a CVD population.

The committee noted that the model was designed to assess a population without CVD, heart failure or diabetes and baseline risks in the model relate to this. Relative treatment effect data used in the model was based on the 2006 and 2011 systematic review of head-to-head studies which included studies where people had CVD.

The committee noted the low cost of anti-hypertensive drugs and that treating hypertension was highly cost effective in people without CVD (increased QALYs and cost saving in most cases as the costs of events avoided offset the cost of treatment). They agreed it was likely to be even more so in people with CVD as the higher baseline risk of CVD events in this population would most likely result in more events avoided.

The most cost-effective first-line anti-hypertensive drug in people without CVD in the model depended on baseline CVD risk, heart failure risk and diabetes risk. CCBs were the most cost-effective option in most people over 55 years and the cost effectiveness of CCBs increased with increasing CVD risk. Given this is was agreed it was unlikely that the increased baseline risk of CVD events in people with CVD would change the overall conclusion of this analysis alone.

Costs and QALYs in people without CVD in the model were similar with CCBs, thiazide-like diuretics and ACE/ARBs and so it was noted that conclusions may be sensitive to differences in relative treatment effects. For example, the previous committees considered exploratory sensitivity analyses in the model where ACE/ARBs were slightly more effective in younger people (under 55 years) and this suggested ACE/ARBs may become the most cost-effective option which supported the committee's different recommendation for younger people. However, the committee concluded that there was not currently evidence to suggest different relative treatment effect in people with CVD compared to people without CVD.

Overall, the committee concluded there was no cost-effectiveness evidence to suggest that recommendations should be different for people with CVD compared to people without CVD.

The committee agreed it was unlikely that there would be a substantial increase in resource use in the NHS in England from not recommending a different algorithm for choice of antihypertensive drugs for people with CVD, after application of disease specific secondary prevention recommendations. This was considered current practice in for most types of CVD. There was some uncertainty about current practice for choice of antihypertensive after a stroke given the current ICSWP stroke guideline recommends that initial antihypertensive treatment for people with stroke/TIA aged 55 or over, or of African or Caribbean origin at any age should be a thiazide-like diuretic or CCB, rather than a CCB being the preferred step 1 option as per NICE NG136. Although hard to quantify given a lack of information about how widely indapamide is prescribed instead of a CCB post-stroke, the committee agreed that any impact on prescribing was likely to be limited given that hypertension treatment usually requires more than one antihypertensive drug. Indapamide is currently more expensive than the lowest cost CCB both are low cost per year. Given these considerations it is considered unlikely there will be a significant impact on costs.

1.1.10.5 Other factors the committee took into account

The committee noted that the approach to this review meant that much of the included evidence was from older studies, using agents or doses that are no longer current practice. However, they also discussed that the overall evidence of no clinically important difference in drug efficacy between those with and without CVD was helpful and supports the message that treating high blood pressure is the priority for reducing the risk of future events.

The committee also discussed the importance of medicines adherence in adults with hypertension, which could be compromised if prescriptions are changed on the basis of a cardiovascular event in a person already being treated for hypertension. This again supports the approach of keeping a single treatment algorithm. However, the committee also emphasised the importance of making treatment decisions on an individual patient basis, taking into account their existing medications and comorbidities when discussing which anti-hypertensive agents to use.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.30 in the NICE guideline.

1.1.12 References

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Appendices

Appendix A – Effectiveness evidence

A.1 Summary of previously included studies on antihypertensive drugs

A.1.1 Summary of studies by comparison

Table 15 to Table 32 outline the populations and available subgroup analyses from previously included studies, ordered by treatment comparison.

Table 15: Summary of studies: thiazide and thiazide-like diuretics versus placebo

Trial	Thiazide	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Range	Mean			Total	TTD	Placebo	
ANBPS[6]	Chlorothiazide[a]	4.0	30–69	50	157/101	3,931	Excluded	-	-	NA
HSCSG[32]	Methychlo-thiazide	2.1	<75	59	167/100	452	All had prior stroke/TIA	Stroke/TIA: 100%	Stroke/TIA: 100%	No
MRC[72]	Bendroflume-thiazide	4.9	35–64	52	161/98	12,951	Stroke: 0.7%; Q wave abnormalities: 1.4%	Stroke: 0.7%; Q wave abnormalities: 1.3%	Stroke: 0.7%; Q wave abnormalities: 1.5%	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group) Multiple logistic regression Stroke: RR 1.65 (1.00-2.69) Coronary event: RR 2.13 (1.56-2.90 CV event: RR 1.94 (1.48-2.54) Total death: RR 2.27 (1.72-3.00)
Oslo[57]	Chlorothiazide[a]	5.5	40–49	45	156/97	785	Not reported	-	-	No
USPHS[95]	Chlorothiazide[a]	>7	<55	44	147/99	422	Excluded	-	-	NA

Trial	Thiazide	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Range	Mean			Total	TTD	Placebo	
VAII[33]	Chlorothiazide[a]	3.2	-	51	164/104	380	Not reported	-	-	No
VA-NHLBI[39]	Chlorthalidone	1.5	21–50	38	-	1,012	Not reported	-	-	No
EWPHE[2, 50, 74]	Hydrochloro-thiazide	4.7	60+	72	183/101	840	Not reported	-	-	No
MRC-O[70]	Hydrochloro-thiazide	5.8	65–74	70	185/91	3,294	MI on ECG: 16%	MI on ECG: 17%	MI on ECG: 16%	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group) Multiple logistic regression Stroke: RR 1.40 (1.01-1.95) CHD: RR 1.50 (1.11-2.03) CV event: RR 1.62 (1.30 -2.03) CV death: RR 1.92 (1.47-2.51) Total death: RR 1.70 (1.37-2.11)
PATS[77]	Indapamide	2.0	-	60	154/93	5,665	All had prior stroke/TIA (but not all had HT)	-	-	No
SHEP-P[48, 80, 81]	Chlorthalidone	2.8	60+	72	172/75	551	Stroke: 1% MI: 4.4% Current angina: 2.8%	Stroke: 1% MI: 5% Current angina: 2%	Stroke: 1% MI: 2% Current angina: 6%	No
SHEP[79, 85, 89, 106]	Chlorthalidone	4.5	60+	72	170/77	4,736	Stroke: 1.4% MI: 4.9%	Stroke: 1.5% MI: 4.9%	Stroke: 1.3% MI: 4.9%	**Proportion with events with and without prior stroke or MI** **Placebo** **CHD HF Stroke**

Trial	Thiazide	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Range	Mean			Total	TTD	Placebo	
										No MI history (n=2207) 125 (5.7%) 90 (4.1%) 153 (6.9%) *MI history (n=116)* 9 (7.7%) 13 (11.2%) 6 (5.2%) *No stroke history (n=2293):* 133 (5.8%) 100 (4.4) 154 (6.7) *Stroke history (n=30):* 1 (3.3%) 3 (10.0) 5 (16.7) **Thiazide** **CHD HF Stroke** *No MI history (n=2196)* 94 (4.3%) 50 (2.3%) 98 (4.3%) *MI history (n=113)* 6 (5.3%) 4 (3.5%) 4 (3.5%) *No stroke history (n=2274):* 98 (4.3%) 53 (2.3) 98 (4.3) *Stroke history (n=35):* 2 (5.8%) 1 (2.9) 4 (11.4)
HYVET[7]	Indapamide (sustained release)	2.1	80+	83.6	173/91	4761	CVD: 11.7% Stroke: 6.8% MI: 3.1% HF: 2.9%	CVD: 11.5% Stroke: 6.7% MI: 3.1% HF: 2.9%	CVD: 12% Stroke: 6.9% MI: 3.2% HF: 2.9%	No

a Chlorothiazide is no longer used in the UK

Table 16: Summary of studies: beta-blockers versus placebo

Trial	Beta-blocker	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Mean	Range			Total	BB	Placebo	
Coope[21]	Atenolol	4.4	69	60–79	196/99	884	Not reported	-	-	No
DUTCH-TIA[105]	Atenolol	2.7	-	-	158/91	1,473	All had TIA or non-disabling ischaemic stroke <3 months ago (only 29% had prior HT)	Stroke/TIA: 100%	Stroke/TIA: 100%	No
IPPPSH[18]	Oxprenolol	3.4	52	40–64	173/108	6,357	Excluded	-	-	No
MRC[72]	Propranolol	4.9	52	35–64	161/98	13,057	Stroke: 0.7%; Q wave abnormalities (MI?): 1.4%	Stroke: 0.7%; Q wave abnormalities (MI?): 1.4%	Stroke: 0.7%; Q wave abnormalities (MI?): 1.5%	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group, including placebo arm) Multiple logistic regression Stroke: RR 1.65 (1.00-2.69) Coronary event: RR 2.13 (1.56-2.90 CV event: RR 1.94 (1.48-2.54) Total death: RR 2.27 (1.72-3.00)
MRC-O[70]	Atenolol	5.8	70	65–74	185/91	3,315	MI on ECG: 16%	MI on ECG: 16%	MI on ECG: 16%	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group, including placebo arm) Multiple logistic regression Stroke: RR 1.40 (1.01-1.95) CHD: RR 1.50 (1.11-2.03) CV event: RR 1.62 (1.30 -2.03) CV death: RR 1.92 (1.47-2.51)

Trial	Beta-blocker	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Mean	Range			Total	BB	Placebo	
										Total death: RR 1.70 (1.37-2.11 arm) Multiple logistic regression Stroke: RR 1.40 (1.01-1.95) CH: RR 1.50 (1.11-2.03) CV event: RR 1.62 (1.30 -2.03) CV death: RR 1.92 (1.47-2.51) Total death: RR 1.70 (1.37-2.11)
STOP-H[25]	Beta-blocker or diuretic	2.1	76	70–84	195/102	1,627	Not reported	-	-	No
TEST[37]	Atenolol	2.3	70	40+	161/89	720	All had stroke/TIA within 3 weeks of study entry (67% major stroke; 20% TIA/ 87% brain infarction; 6% ICH; 7% unknown)	History of: major stroke: 14.7% TIA: 14.9% MI: 9.8% Angina: 16.7% HF treatment: 5.8%	History of: major stroke: 18.1% TIA: 14.5% MI: 9.8% Angina: 14.8% HF treatment: 2.7%	No

Table 17: Summary of studies: ACE inhibitor versus placebo

Trial	ACE inhibitor	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Range	Mean			Total	ACE inhibitor	Placebo	
PROGRESS[64]	Perindopril	3.9	26–91	64	147/86	6,105	All had stroke or TIA Only 48% had hypertension	CHD: 16%	CHD: 16%	HT vs non-HT for stroke and major vascular events **Stroke** Relative risk reduction 32 (17-44)% in HT vs 27 (8-42)% in non-HT **Major vascular events** Relative risk reduction 29 (16-40)% in HT vs 24 (9-37)% in non-HT

Table 18: Summary of studies: ARB versus placebo

Trial	ARB	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline			Additional analysis
			Range	Mean			Total	ARB	Placebo	
SCOPE[46, 62]	Candesartan	3.7	70–89	76	166/90	4,964	MI: 4.5% Stroke: 3.9%	MI: 4.5% Stroke: 3.9%	MI: 4.6% Stroke: 3.9%	No

Table 19: Summary of studies: CCB versus placebo

Trial	CCB	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline	Additional analysis
			Range	Mean				
SYST-EUR[3, 19, 40, 98-100]	Nitrendipine	23	60+	70	174/86	4,695	Stroke: 4.1% MI: 11.6%	Presence vs absence of CVD complications as predictor of outcome regardless of treatment group **Unadjusted HR**

Trial	CCB	Follow-up, yrs	Age in years		Baseline BP, mmHg	Number enrolled	CVD at baseline	Additional analysis
			Range	Mean				
							CHD: 29.3% Cerebrovascular disease: 3.2% (not reported by group)	**Total mortality**: 2.52 (1.98-3.22) **CV mortality**: 2.82 (2.01-3.95) **Fatal and nonfatal stroke**: 1.69 (1.18-2.42) **Fatal and nonfatal cardiac events**: 2.66 (2.02-3.50) **Adjusted HR** (covariates: treatment group, sex, age, increase in SBP 10mmHg, smoking, recruitment from Eastern Europe) **Total mortality**: 1.86 (1.45-2.38) **CV mortality**: 2.17 (1.54-3.05) **Fatal and nonfatal stroke**: 1.44 (1.00-2.07) **Fatal and nonfatal cardiac events**: 2.27 (1.72-2.99)

Head-to-head trials

Table 20: Summary of studies: CCB versus ACE-inhibitor

Trial	CCB	ACE inhibitor	Number enrolled	CVD at baseline			Additional analysis
				Total	ACE inhibitor	CCB	
ALLHAT[5] [6, 75, 76, 82]	Amlodipine	Lisinopril	18,102	52% atherosclerotic CVD	MI or stroke: 22.7%	MI or stroke: 23.2% Coronary	Event rates in those with and without CHD at baseline **CHD at baseline** **Amlodipine** **Lisinopril** **No CHD at baseline** **Amlodipine** **Lisinopril**

Trial	CCB	ACE inhibitor	Number enrolled	CVD at baseline			Additional analysis
				Total	ACE inhibitor	CCB	
				25% CHD	Coronary revascularisation: 13.5% Other atherosclerotic CVD 23.8% Major ST depression or T-wave inversion: 10.5% CHD: 25.3%	revascularisation: 12.2% Other atherosclerotic CVD 23.7% Major ST depression or T-wave inversion: 10.5% CHD: 25%	**(n=2202) (n=2270) (n=6777) (n=6715)** CHD 282 (16.1) 300 (17.0) 507 (9.6) 494 (9.4) Mortality 358 (19.8) 418 (21.6) 882 (15.7) 883 (15.7) Stroke 105 (6.5) 138 (7.2) 268 (5.0) 314 (6.0) HF 250 (15.1) 231 (12.7) 453 (8.7) 377 (7.4) Angina 467 (24.8) 469 (24.3) 474 (8.5) 538 (9.8) Revasc 308 (16.9) 319 (18.0) 410 (7.7) 394 (7.5) PAD 109 (5.8) 102 (5.8) 153 (2.9) 207 (3.9) **There were no significant interactions between treatment (lisinopril** vs **amlodipine) and CHD history (yes** vs **no) for any of these outcomes reported in the study.**
JMIC-B[111, 112]	Nifedipine (long-acting)	Enalapril, imidapril, or lisinopril	1650	All had CAD Angina: 65%, MI: 42%, Asymptomatic myocardial ischemia: 12%	Angina: 61.7%, MI: 46.4%, Asymptomatic myocardial ischemia: 12.7%	Angina: 68.4%, MI: 38.0%, Asymptomatic myocardial ischemia: 11.5%	Relative risk CCB vs ACE inhibitor adjusted for sex, age, history of myocardial infarction and angina pectoris using the Cox proportional hazard model. **Overall incidence of cardiac events,** History of MI: 0.91 (0.63-1.51) No history of MI: 1.26 (0.85-1.87) **Hospitalization for angina pectoris** History of MI: 0.42 (0.22-0.80) No history of MI: 1.29 (0.76-2.19) - CCB better if history of MI (58% risk reduction vs ACEI)

Trial	CCB	ACE inhibitor	Number enrolled	CVD at baseline			Additional analysis
				Total	ACE inhibitor	CCB	
STOP-H2[24, 44, 45, 59]	Felodipine or isradipine	Enalapril, or lisinopril	4401	MI 4.2%; IHD: 9.3%, stroke: 5.0%; CHF: 2.9%; AF 6.3%; other CVD: 5.6%	MI 3.0%; IHD: 10.6%, stroke: 4.3%; CHF: 3.0%; AF 4.3%; other CVD: 6.8%	MI 2.6%; IHD: 7.8%, stroke: 3.5%; CHF: 2.9%; AF 5.6%; other CVD: 4.3%	No

Table 21: Summary of studies: ARB versus CCB

Trial	ARB	CCB	Number enrolled	CVD at baseline			Additional analysis
				Total	ARB	CCB	
VALUE[52]	Valsartan	Amlodipine	15,245	CHD: 45.6%, PAD: 13.8%, Stroke or TIA: 19.8%	CHD: 45.6%, PAD: 13.8%, Stroke or TIA: 19.8%	CHD: 46.0%, PAD: 14.0%, Stroke or TIA: 19.8%	No

Table 22: Summary of studies: ARB versus thiazide-like diuretic

Trial	ARB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	ARB	TTD	
ALLHAT[66]	Doxazosin	Chlorthalidone	24,335	45% atherosclerotic CVD	45.6% atherosclerotic CVD	45.2% atherosclerotic CVD	No

Table 23: Summary of studies: ACE inhibitor versus thiazide or thiazide-like diuretics

Trial	ACE inhibitor	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	ACE inhibitor group	Thiazide or thiazide-like diuretic group	
ALLHAT [75]	Lisinopril	Chlorthalidone	24,309	Atherosclerotic CVD – 51.8%	MI or stroke: 22.7% Coronary revascularisation: 13.5% Other atherosclerotic CVD 23.8% Major ST depression or T-wave inversion: 10.5% CHD: 25.3%	MI or stroke: 23.5% Coronary revascularisation: 13.0% Other atherosclerotic CVD 23.6% Major ST depression or T-wave inversion: 10.4% CHD: 26.0%	No
PHYLLIS[115]	Fosinopril	Hydrochlorothiazide	508	Not stated	-	-	No
ANBP2[110]	Enalapril	Hydrochlorothiazide	6083	CHD: 8% Cerebrovascular disease: 5%	CHD: 8% Cerebrovascular disease: 5%	CHD: 8% Cerebrovascular disease: 4%	No

Table 24: Summary of studies: CCB versus thiazide or thiazide-like diuretics

Trial	CCB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB group	Thiazide or thiazide-like diuretics	
ALLHAT[75]	Amlodipine	Chlorthalidone	24,303	Atherosclerotic CVD – 51.4%	MI or stroke: 23.2% Coronary revascularisation: 12.2% Other atherosclerotic CVD 23.7% Major ST depression or T-wave inversion: 10.1% CHD: 24.5%	MI or stroke: 23.5% Coronary revascularisation: 13.0% Other atherosclerotic CVD 23.6% Major ST depression or T-wave inversion: 10.4% CHD: 26.0%	No

Trial	CCB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB group	Thiazide or thiazide-like diuretics	
INSIGHT [14, 15]	Nifedipine	Co-amilozide	6321	CHD: 6.4% Prior MI: 6.1% PVD: 5.6%	CHD: 6.6% Prior MI: 6.2% PVD: 5.7%	CHD: 6.2% Prior MI: 5.9% PVD: 5.5%	Angina, PVD, MI, but not diabetes, predictors of outcome (composite of death from cardio or cerebrovascular cause, nonfatal stroke MI and heart failure) in unadjusted analysis on full study cohort (not randomised groups) Unadjusted HR (95% CI): Angina 1.64 (1.19-2.26) PVD 1.72 (1.25-2.36) MI 1.96 (1.44-2.67) Diabetes 1.47 (1.16-1.86)
MIDAS [11, 17]	Isradipine	Hydrochlorothiazide	883	MI 1.9%; angina 0.7%; coronary bypass 1.5%	MI 1.4%; angina 1.1%; coronary bypass 0.7%	MI 2.5%; angina 0.2%; coronary bypass 2.3%	No
NICS-EH [54, 88]	Nicardipine	Trichlormethiazide	414	Excluded	-	-	No
VHAS [93, 116]	Verapamil	Chlorthalidone	1414	5% cardiac or cerebrovascular disease; 30%	Cardiac or cerebrovascular disease: 5.1%	Cardiac or cerebrovascular disease: 4.8%	-

Trial	CCB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB group	Thiazide or thiazide-like diuretics	
				carotid plaques			
THAI elderly[104]	Amlodipine	Hydrochlorothiazide	200	6% IHD	6% IHD	6% IHD	No
Sareli et al. 2001[94]	Nifedipine or verapamil	Hydrochlorothiazide	409	Not stated	-	-	No
SHELL[67]	Lacidipine	Chlorthalidone	1882	Not stated	-	-	No

Table 25: Summary of studies: Beta blocker versus thiazide diuretics

Trial	BB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	BB	Thiazide diuretic	
HAPPHY[109]	Atenolol or metoprolol	Bendroflumethiazide or hydrochlorothiazide initially	6569	CVD excluded	-	-	No
MRC[72]	Propanolol	Bendroflumethiazide	8700	Stroke: 0.7%; Q wave abnormalities (MI?): 1.4%	Stroke: 0.7%; Q wave abnormalities (MI?): 1.4%	Stroke: 0.7%; Q wave abnormalities (MI?): 1.3%	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group, including placebo arm) Multiple logistic regression Stroke: RR 1.65 (1.00-2.69) Coronary event: RR 2.13 (1.56-2.90 CV event: RR 1.94 (1.48-2.54) Total death: RR 2.27 (1.72-3.00)
MRC-O[70]	Atenolol	Hydrochlorothiazide plus amiloride	2183	16% had evidence of MI on ECG	15% evidence of MI on ECG	17% evidence of MI on ECG	Ischaemic vs non-ischaemic ECG changes (irrespective of treatment group, including placebo arm)

Trial	BB	TTD	Number enrolled	CVD at baseline			Additional analysis
				Total	BB	Thiazide diuretic	
							Multiple logistic regression Stroke: RR 1.40 (1.01-1.95) CHD: RR 1.50 (1.11-2.03) CV event: RR 1.62 (1.30 -2.03) CV death: RR 1.92 (1.47-2.51) Total death: RR 1.70 (1.37-2.11)

Table 26: Summary of studies: ARB versus beta blocker

Trial	ARB	BB	Number enrolled	CVD at baseline			Additional analysis
				Total	ARB	BB	
LIFE[22, 60, 61 30, 42, 90, 107, 108]	Losartan	Atenolol	9193	Any vascular disease: 25% Coronary heart disease 15.9%; cerebrovascular disease 8%; AF: 3.5%; PVD: 5.7%; HF: 1.8%	Any vascular disease: 26% Coronary heart disease 17%; cerebrovascular disease 8%; AF: 3%; PVD: 6%;	Any vascular disease: 24% Coronary heart disease 15%; cerebrovascular disease 8%; AF: 4%; PVD: 5%;	

Table 27: Summary of studies: calcium channel blocker versus beta blocker

Trial	CCB	BB	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB	BB	
ASCOT[20, 26]	Amlodipine-based	Atenolol-based	19257	Stroke/TIA: 11%	Stroke/TIA: 11%	Stroke/TIA: 11%	**Unadjusted HR for total CV events and procedures** Prior vascular disease: 0.80 (0.70-0.92)

Trial	CCB	BB	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB	BB	
				ECG abnormalities other than LVH: 23% PVD: 6% Other CVD: 6%	ECG abnormalities other than LVH: 23% PVD: 6% Other CVD: 6%	ECG abnormalities other than LVH: 23% PVD: 6% Other CVD: 5%	No prior vascular disease: 0.85 (0.78-0.92) **N with event** Prior vascular disease: CCB: 360 (23%); BB: 443 (28%) No prior vascular disease: CCB: 1002 (12%); BB: 1159 (14%)
ELSA[114]	Lacidipine	Atenolol	2334	Not reported	-	-	No
INVEST[78]	Verapamil sustained release	Atenolol	22,576	100% CAD (MI, angina, CABG/PCI) 5% stroke, HF, PVD	MI: 32.1% Prior MI/abnormal angiogram: 52.6% Angina: 66.2% CABG or PCI: 27.3% Stroke: 5.3% HF: 5.5% PVD: 11.9%	MI: 31.8% Prior MI/abnormal angiogram: 53.3% Angina: 67% CABG or PCI: 27.3% Stroke: 5.0% HF: 5.6% PVD: 12%	**RR for first event** (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) No MI: 0.99 (0.89-1.11) MI: 0.95 (0.85-1.07) No HF: 0.95 (0.87-1.03) HF: 1.21 (0.99-1.47) No revascularisation: 0.99 (0.89-1.09) Revascularisation: 0.96 (0.85-1.09) **N with event** No MI: CCB - 624/7645; BB - 633/7713 MI: CCB - 495/3622; BB - 517/3596 No HF: CCB - 956/10 648; BB - 1011/10672 HF: CCB - 163/619; BB - 139/637 No revascularisation: CCB - 690/8188; BB - 702/8222

Trial	CCB	BB	Number enrolled	CVD at baseline			Additional analysis
				Total	CCB	BB	
							Revascularisation: CCB - 429/3079; BB - 448/3087

Table 28: Summary of studies: ACE-inhibitor versus angiotensin-II receptor antagonist (2011)

Trial	ACE inhibitor	ARB	Number enrolled	CVD at baseline			Additional analysis
				Total	ACE inhibitor	ARB	
CORD IB[97]	Ramipril	Losartan	3813	IHD 25.4%, MI 11.7%, HF 5.7%	IHD 26.7%, MI 13.0%, HF 6.0%	IHD 24.1%, MI 10.4%, HF 5.3%	No
ONTARGET[113]	Ramipril	Telmisartan	25,620	CVD: 91.3%	CAD: 74.4% MI: 48.3% Stable angina: 35.4% Unstable angina: 14.7% Stroke/TIA: 21.0% CABG: 21.7%	CAD: 74.5% MI: 49.3% Stable angina: 34.6% Unstable angina: 15.2% Stroke/TIA: 20.6% CABG: 22.5%	Telmisartan vs ramipril for death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure Incidence of primary outcome in ramipril group CVD (n=15,672): 16.8% No CVD (n=1486): 13.1% p for interaction 0.79
Tedesco 2006[102]	Enalapril	Losartan	560	0% MI or stroke	-	-	No

Table 29: Summary of studies: Diuretic head-to-head comparisons

Study	N	Intervention	Control	Follow-up	Results	CVD at baseline	Additional analysis
Thiazide-like diuretics vs thiazide diuretics							
Bowlus 1964[12]	29	Chlorthalidone (50mg/day)	Hydrochlorothiazide (100 mg/day	6 weeks treatment, 2 weeks washout	NS difference in BP between groups.	Not stated	No

Study	N	Intervention	Control	Follow-up	Results	CVD at baseline	Additional analysis
Ernst, 2006[38]	30	Chlorthalidone (12.5mg/day) force titrated to 25mg/day	Hydrochlorothiazide (25mg/day) force titrated to 50mg/day	8 weeks treatment, 4 weeks washout, 8 weeks treatment	NS difference (office BP and 24hr ABPM) between groups.	Not stated	No
Finnerty, 1976[41]	54	Chlorthalidone (50mg/day plus placebo)	Hydrochlorothiazide (100mg/day)	2 weeks no treatment, followed by 4 weeks of treatment in either arm.	NS difference in BP between groups.	Not stated	No
Kreeft, 1984[53]	17	Indapamide (2.5mg/day)	Hydrochlorothiazide (50mg/day)	2 months placebo run-in, 12 weeks TD drug, 2 months placebo washout, 12 weeks alternate TD drug.	NS difference in BP between groups.	CVD excluded	No
Plante, 1988[83]	47	Indapamide (2.5mg/day)	Hydrochlorothiazide (50 mg/day)	48 weeks	IND better for reduced BP (no P value reported) and was less likely to be associated with hypokalaemia.	Not stated	No
Plante, 1983[84]	24	Indapamide (2.5mg/day)	Hydrochlorothiazide (50 mg/day)	4-6 washout placebo period, followed by 12 weeks active therapy.	IND better for reduction in DBP in the recumbent position	Not stated	No
Spence, 2000[96]	39	Indapamide (2.5mg/day)	Hydrochlorothiazide (25 mg/day)	6 months	NS difference in BP between groups	Not stated	No
Brandao, 2010[13]	94	Indapamide (1.5 mg/day)	Hydrochlorothiazide (25 mg/day)	12 weeks Previously untreated patients. Addition of ACEi at 6	NS difference in BP (office or ABPM) between groups	Not stated	No

Study	N	Intervention	Control	Follow-up	Results	CVD at baseline	Additional analysis
				weeks if target BP not met.			
Emeriau, 2001[36]	524	Indapamide (SR) (1.5 mg/day)	Hydrochlorothiazide (25 mg/day) Amlodipine (5 mg/day)	4 week washout placebo period; 12 weeks treatment	Similar reduction in BP between groups (equivalence test)	Not stated	No
Elliot, 1991[34]	11	Indapamide (2.5mg/day)	Hydrochlorothiazide (25 mg/day)	28 days	NS difference in BP between groups.	Not stated	No
Alem, 2008[1]	26	Indapamide (2.5mg/day)	Bendroflumethiazide (2.5 mg/day)	28 days	Both IND and BDZ reduced BP to a significant degree.	All had history of TIA or stroke but hypertension diagnosis not required	No
Bing, 1981[9]	20	Indapamide (2.5mg/day)	Bendroflumethiazide (5 mg/day)	22 weeks	Equivalent fall in BP in both groups	Not stated	No
Thiazide-like diuretics vs thiazide-like diuretics							
Rakić, 2002[87]	80	Indapamide (2.5mg/day)	Chlorthalidone (25mg/day) NIC (60mg/day) PPL (120mg/day)	6 months	Significant decreases in BP in all groups	Not stated	No
Hatt, 1975[47]	36	Indapamide (5mg/day)	Chlorthalidone (100mg/day)	10 days washout, followed by 90 day crossover	IND better % reduction in DBP.	Not stated	No
Thiazide diuretics vs thiazide diuretics							
Anonymous, 1984[49]	44	Hydrochlorothiazide (12.5mg/day)	Bendroflumethiazide (12.5mg/day)	12 months	NS difference in BP between groups.	Not stated	No

Table 30: Summary of studies: combination vs monotherapy (2019)

Study	N	Combination	Monotherapy	CVD at baseline	Additional analysis
Asmar 2001[4, 5, 27, 63, 68] REASON trial	471	Perindopril 2 mg plus indapamide 0.625 mg (n=235)	Atenolol 50 mg (n=234)	Not stated	No
Dahlof 2005[23] PIXCEL trial	679	Perindopril 2 mg plus Indapamide 0.625 mg (n=341)	Enalapril 10 mg (n=338)	Not stated	No
Mogensen 2003[71] PREMIER trial	481	Perindopril 2 mg plus indapamide 0.625 mg (n=237)	Enalapril 10 mg (n=244)	Not stated	No

Table 31: Summary of studies: ACE inhibitor + CCB versus ACE inhibitor + diuretic for second line therapy (2011)

Study	N	Intervention (ACE inhibitor + CCB)	Control (ACE inhibitor + diuretic)	CVD at baseline		Additional analysis
				ACE inhibitor + CCB	ACE inhibitor + diuretic	
Jamerson 2008[51] ACCOMPLISH	11,506	Benazepril (20 then 40mg/day) + amlodipine (5 mg/day)	Benazepril (20 then 40mg/day) + hydrochlorothiazide	MI: 23.3%, Stroke: 13.3% unstable angina hosp: 11.4%, coronary revascularisation: 35.6%	MI: 23.8%, Stroke: 12.8% unstable angina hosp: 11.6%, coronary revascularisation: 36%	No

Table 32: Summary of studies: non-randomised evidence in resistant hypertension (2011)

Study	N	Intervention	Comparison	Follow-up	Results	CVD at baseline	Additional analysis
Rodilla 2009[92]	198	Spironolactone	Doxazosin	Until change of treatment/ target blood pressure maintained	Spironolactone best (decreased home or ambulatory SBP and DBP)	Not stated	No

Study	N	Intervention	Comparison	Follow-up	Results	CVD at baseline	Additional analysis
Mahmud 2005[65]	69	Previously untreated-spironolactone/bendroflumethiazide	4th line Spironolactone	3-4 months	Spironolactone effective in reducing BP when used as a 4th line drug	Not stated	No
Chapman 2007[20]	1411	ASCOT trial patients an a-HT regimen based on either Atenolol or amlodipine Plus addition of Spironolactone	ASCOT trial patients on a-HT regimen based on either Atenolol or amlodipine	Median 5.5 years	Addition of spironolactone effective in reducing BP	Not stated	No
De Souza 2010[28]	236	Spironolactone	Before vs. after Spironolactone	12 months (Median 15 months, IQR 13-20 months)	Spironolactone effective in reducing 'office' and ambulatory blood pressure.	51.7%	% with CVD similar across different response groups SBP response ≤10%: 51.9% CVD SBP response >10%: 51.1% CVD P=0.99 DBP response ≤10%: 52.2% CVD DBP response >10%: 50.6% CVD P=0.88
Lane 2007[55]	133	Spironolactone	Before vs. after Spironolactone	6 months	Spironolactone effective in reducing SBP and DBP	Not stated	No
Gaddam 2010[43]	12	Spironolactone	Before vs. after Spironolactone	8 weeks	Addition of spironolactone effective in reducing SBP and DBP	Not stated	No

A.1.2 Ethnicity

In the 2011 version of the guideline (CG127), a separate search was conducted to find evidence on drug efficacy in people of black African or African-Caribbean family origin. No information on the proportion with CVD was available within the ethnicity-based subgroup analysis (see Table 33).

Table 33: Summary of studies: ACE inhibitor versus CCB or diuretic

Trial	ACE inhibitor	CCB	Diuretic	ARB	Number enrolled	CVD at baseline	Additional analysis
ALLHAT[5, 6, 82]	Lisinopril	Amlodipine	Chlorthalidone	Doxazosin	42,418	52% atherosclerotic CVD 25% CHD	Subgroup analysis for angioedema in black and non-black people Proportion with CVD in black/non-black subgroups not reported

A.1.3 Age – younger people (≤55 years)

In the absence of clinical outcomes data in younger people, the recommendation to choose ACE inhibitor or angiotensin-II receptor blocker as step 1 therapy was based on data suggesting that an ACE inhibitor (or angiotensin II receptor blocker) was likely to produce the most effective blood pressure lowering as initial therapy in younger patients. See Table 34.

Three studies and an age-stratified analysis from a fourth study compared blood pressure response across various drug classes and identified ACE inhibitors and beta-blockers as more effective at lowering blood pressure in younger people, when compared to calcium channel-blockers or thiazide-type diuretics.

Table 34: Summary of studies in younger people : ACE inhibitor versus CCB or diuretic

Trial	Study design	Intervention and comparison	Number enrolled	Age	CVD at baseline	Comments
Materson 1993[69]	RCT	Placebo or ACE inhibitor, BB, thiazide diuretic, CCB, ARB, or centrally-acting alpha-agonist	1292	Mean 59 (age stratified <60 and 60+ years)	Not reported	Only included men

Trial	Study design	Intervention and comparison	Number enrolled	Age	CVD at baseline	Comments
Dickerson 1999[31]	Crossover RCT UK	Four monthly cycles of treatment with an ACE inhibitor (A), beta-blocker (B), calcium-channel blocker (C), and diuretic (D).	56	Range: 22-51 years	Not reported	-
Deary 2002[29]	Crossover RCT	ACE-I, CCB, ARB, BB, thiazide diuretic, placebo	34	Range: 28-55 years	Not reported	-
ASCOT steering committee 2006	Personal communication	Age stratified analysis		-	-	Data not reported in guideline – not retrievable

A.1.4 Age – older (>80 years)

Key studies supporting initiation of antihypertensives in those aged over 80 years generally included older people who were fit and active and had low levels of comorbidities (see Table 35). The committee recommended that treatment decisions in those aged ≥80 years should be based on the realistic expectations of clinical benefit from treatment in the context of other comorbidities which might limit life expectancy. Furthermore, the committee recommended that for older patients who are already receiving antihypertensive treatment when they reach the age of 80 years, the evidence supports continuation of treatment.

Table 35: Summary of studies in older people: active treatment versus placebo

Trial	Study design	Intervention	Comparison	Number pts.	Mean (SD) age, years	CVD at baseline	Comments
Bejan-Angoulvant 2010[8]	Systematic review and meta-analysis	First: diuretic, BB or CCB	Placebo or no treatment	Subgroups from 6 studies: 1573	83 (3)	Prior MI: 5.0% Prior stroke: 4.0%	Included subgroups from SHEP, SHEP-P, SYST-EUR, EWPHE, STOP, and Coope 1986 as well as the full HYVET and HYVET pilot trials
HYVET[7]	RCT	First: diuretic	Placebo	3845	83.6 (3.2)	Total CVD: 12%	

Trial	Study design	Intervention	Comparison	Number pts.	Mean (SD) age, years	CVD at baseline	Comments
						Prior MI: 3.1% Prior stroke: 6.8%	
HYVET PILOT[16]	RCT	First: diuretic or ACE inhibitor	No treatment	1283	83.8 (3)	Prior MI: 3.0% Prior stroke: 4.5%	Reported predictive value of previous and MI and stroke for having an event. HR (95% CI) : **Prior MI vs no MI** Total mortality – 1.34 (0.47 to 3.83) CV mortality - 1.59 (0.55 to 4.61) Cardiac mortality - 4.16 (1.32 to 13.04) **Prior stroke vs no stroke** Total mortality – 1.24 (0.49 to 3.12) CV mortality - 1.58 (0.62 to 3.99) Fatal stroke - 1.57 (0.37 to 6.89) Previous MI predicted cardiac death but previous stroke did not predict a stroke death (interaction with treatment not reported)

A.2 Studies with data on the interaction between CVD history and treatment outcomes

A.2.1 New evidence extractions to inform interactions

The evidence tables in this section present data not previously analysed within the guideline. They are limited to previously included studies that provide additional data to inform whether the presence versus absence of a specific cardiovascular disease history modifies the antihypertensive drug treatment effect. Please see section A.2.2 for further study details.

Reference	ALLHAT - Leenen 2006[56]
Study type and analysis	Randomized double-blind clinical trial Kaplan–Meier method and Cox-proportional hazards regression model were used for analysis.
Number of participants and characteristics	N= 18105 History of CHD: 4472 **Inclusion criteria:** Age > 55 years; untreated systolic (140 to 180 mm Hg) and/or diastolic (90 to 110 mm Hg) hypertension, or treated hypertension (<160/100 mm Hg on 1 to 2 antihypertensive drugs at visit 1) >1 additional risk factor for CHD. **Exclusion criteria:** Not reported **Study level characteristics** % Male: 53% Mean age (SD): 66.7 (SD 7.7) Ethnicity: Blacks (35.5%), Non-blacks (64.5%) Blood pressure at entry: 146/84 mmHg Pre-existing CVD diagnoses: CHD (24.7%) Type 2 diabetes: 36% Chronic kidney disease: Not reported **Subgroup level characteristics:** baseline characteristics not reported separately for those with and without CVD **Population source**: Not reported
Randomised treatments	Intervention: Amlodipine (N= 9048) Dosages were 2.5, 5, and 10 mg per day Comparison: Lisinopril (N = 9057) Dosages were 10, 20, and 40 mg per day Concomitant therapy: step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) agents used when necessary.

Reference	ALLHAT - Leenen 2006[56]
CVD history (subgroups reported)	Coronary heart disease history
Confounders	For interactions between treatment (lisinopril vs amlodipine) and CHD history (yes vs no): unclear how analysed : probably testing for treatment–covariate interaction with an unadjusted Cox proportional hazards regression model.
Outcomes and effect sizes	Event rates in those with and without CHD at baseline **CHD at baseline** / **No CHD at baseline** **Amlodipine (n=2202)** / **Lisinopril (n=2270)** / **Amlodipine (n=6777)** / **Lisinopril (n=6715)** CHD 282 (16.1) / 300 (17.0) / 507 (9.6) / 494 (9.4) Mortality 358 (19.8) / 418 (21.6) / 882 (15.7) / 883 (15.7) Stroke 105 (6.5) / 138 (7.2) / 268 (5.0) / 314 (6.0) HF 250 (15.1) / 231 (12.7) / 453 (8.7) / 377 (7.4) Angina 467 (24.8) / 469 (24.3) / 474 (8.5) / 538 (9.8) Revasc 308 (16.9) / 319 (18.0) / 410 (7.7) / 394 (7.5) PAD 109 (5.8) / 102 (5.8) / 153 (2.9) / 207 (3.9) **There were no significant interactions between treatment (lisinopril** vs **amlodipine) and CHD history (yes** vs **no) for any of these outcomes reported in the study.**
Comments	High attrition bias (withdrawals greater than event rate). Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status. No indirectness noted

Reference	ASCOT - Dahlof 2005[26]
Study type and analysis	Multicentre, prospective, randomised controlled trial. Kaplan-Meier method was used for all major endpoints.
Number of participants	N= 19257 History of Stroke and TIA= 2113

Reference	ASCOT - Dahlof 2005[26]
and characteristics	**Inclusion criteria:** 1. Aged 40–79 years 2. untreated hypertension (systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both) 3. or treated hypertension (systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both) 4. In addition, at least three of the following: - cardiovascular risk factors left-ventricular hypertrophy (detected by electrocardiogram or echocardiogram). - other specified abnormalities on electrocardiogram, - type 2 diabetes. - peripheral arterial disease. - previous stroke or transient ischaemic attack. - male sex - age 55 years or older. - microalbuminuria or proteinuria. - smoking. - ratio of plasma total cholesterol to HDL-cholesterol of six or higher. - family history of premature CHD. **Exclusion criteria:** 1. Previous myocardial infarction 2. Currently treated angina 3. A cerebrovascular event within the previous 3 months 4. Fasting triglycerides higher than 4·5 mmol/L 5. Heart failure 6. Uncontrolled arrhythmias 7. Any clinically important haematological or biochemical abnormality on routine screening **Study level characteristics** % Male: 77% Mean age (SD): 63 (SD 8.5)

Reference	ASCOT - Dahlof 2005[26]
	Ethnicity: White (95%) Blood pressure at entry: 164/95 mmHg Pre-existing CVD diagnoses: Stroke, TIA, LVH Type 2 diabetes: Diabetes 27% (type not reported) Chronic kidney disease: Not reported **Subgroup level characteristics:** baseline characteristics not reported separately for those with and without CVD **Population source**: not reported
Randomised treatments	**Intervention**: Amlodipine-based regimen (N=9639) Step 1 Amlodipine 5 mg Step 2 Amlodipine 10 mg Step 3 Amlodipine 10 mg + Perindopril 4 mg Step 4 Amlodipine 10 mg + Perindopril 8 mg (2x4 mg) Step 5 Amlodipine 10 mg + Perindopril 8 mg (2x4 mg) + Doxazosin gastrointestinal transport system 4 mg Step 6 Amlodipine 10 mg + Perindopril 8 mg (2x4 mg) + Doxazosin gastrointestinal transport system 8 mg **Comparison**: Atenolol-based regimen (N=9618) Step 1 Atenolol 50 mg Step 2 Atenolol 100 mg Step 3 Atenolol 100 mg + Bendroflumethiazide 1·25 mg + potassium Step 4 Atenolol 100 mg + Bendroflumethiazide 2·5 mg + Potassium Step 5 Atenolol 100 mg + Bendroflumethiazide 2·5 mg + Potassium+ Doxazosin gastrointestinal transport system 4 mg Step 6 Atenolol 100 mg + Bendroflumethiazide 2·5 mg + Potassium+ Doxazosin gastrointestinal transport system 8 mg
CVD history (subgroups reported)	History of vascular disease
Confounders	Not reported
Outcomes and effect sizes	**Unadjusted HR for total CV events and procedures** Prior vascular disease: 0.80 (0.70-0.92) No prior vascular disease: 0.85 (0.78-0.92)

Reference	ASCOT - Dahlof 2005[26]
	N with event Prior vascular disease: CCB: 360 (23%); BB: 443 (28%) No prior vascular disease: CCB: 1002 (12%); BB: 1159 (14%)
Comments	Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status. No indirectness noted

Reference	INVEST - Pepine 2003[78]
Study type and analysis	Prospective, randomized, open blinded, end-point evaluation design. Kaplan Meier survival analysis used for primary and main secondary outcome. Primary outcome analysed both adjusted and unadjusted for pre specified covariates. Cox-proportional hazard model used for sub-group analysis.
Number of participants and characteristics	N= 22576 100% CAD (MI, angina, CABG/PCI) Myocardial infarction (32%) Abnormal angiogram (39%) Prior MI or abnormal angiogram (53%) Concordant stress test abnormalities (21%) Angina pectoris (67%) Unstable Angina >1month ago (11%) CABG >1 (16%), PCI >1 (15%) CABG or PCI (27%) Stroke (5%) Left ventricular hypertrophy (22%) Arrhythmia (7%) Heart failure (class I-III) (5%) Peripheral vascular disease (12%) **Inclusion criteria:** Age > 50 years, Coronary artery disease and essential hypertension, requiring drug therapy.

Reference	INVEST - Pepine 2003[78]
	Exclusion criteria: Patients taking BB within two weeks of randomization, or for MI that occurred in previous 12 months to avoid withdrawal phenomenon **Study level characteristics** % Male: **Mean age (SD):** 66 (SD 9.75) **Ethnicity**: White (48.4%), Black (13.4%), Hispanic (35.6%), Asian (0.7%), Multiracial (1.9%) **Blood pressure at entry**: Systolic (149.5), Diastolic (86.3) **Pre-existing CVD diagnoses**: Myocardial infarction (32%), Abnormal angiogram (39%), Prior MI or abnormal angiogram (53%), Concordant stress test abnormalities (21%), Angina pectoris (67%), Unstable Angina >1month ago (11%), CABG >1 (16%), PCI >1 (15%), CABG or PCI (27%), Stroke (5%), Left ventricular hypertrophy (22%), Arrhythmia (7%), Heart failure (class I-III) (5%), Peripheral vascular disease (12%) **Type 2 diabetes**: Diabetes (28%) **Chronic kidney disease**: Renal impairment (2%) **Subgroup level characteristics:** baseline characteristics not reported separately for those with and without CVD Patients were recruited from 862 selected sites in 14 countries
Randomised treatments	Intervention: CAS group - Verapamil (N = 11267) Step 1: Verapamil sustained release 240mg/d Step 2: Verapamil sustained release 240mg/d + Trandolapril 2mg/d Step 3: Verapamil Sustained Release, 180 mg Twice Daily + Trandolapril, 2 mg Twice Daily Step 4: Verapamil Sustained Release, 180 mg Twice Daily + Trandolapril, 2 mg Twice Daily + Hydrochlorothiazide, 25 mg/d Step 5: Maximum Tolerated Dose, and/or Add Non-study Antihypertensive Medication Comparison: NCAS group - Atenolol (N = 11309) Step 1: Atenolol 50mg/d Step 2: Atenolol, 50 mg/d + Hydrochlorothiazide, 25 mg/d Step 3: Atenolol, 50 mg Twice Daily + Hydrochlorothiazide, 25 mg Twice Daily Step 4: Atenolol, 50 mg Twice Daily + Hydrochlorothiazide, 25 mg Twice Daily + Trandolapril, 2 mg/d Step 5: Maximum Tolerated Dose, and/or Add Non-study Antihypertensive Medication

Reference	INVEST - Pepine 2003[78]
CVD history (subgroups reported)	History of MI or history of heart failure
Confounders	In the analysis of treatment comparisons: Age Race Sex Previous MI Previous heart failure No formal analysis of the interaction between treatment and CVD history
Outcomes and effect sizes	**RR for first event** (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) No MI: 0.99 (0.89-1.11) MI: 0.95 (0.85-1.07) No HF: 0.95 (0.87-1.03) HF: 1.21 (0.99-1.47) No revascularisation: 0.99 (0.89-1.09) Revascularisation: 0.96 (0.85-1.09) **N with event** No MI: CCB - 624/7645; BB - 633/7713 MI: CCB - 495/3622; BB - 517/3596 No HF: CCB - 956/10 648; BB - 1011/10672 HF: CCB - 163/619; BB - 139/637 No revascularisation: CCB - 690/8188; BB - 702/8222 Revascularisation: CCB - 429/3079; BB - 448/3087
Comments	Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.

Reference	INVEST - Pepine 2003[78]
	No indirectness noted

Reference	JMIC-B - Yui 2004[112]
Study type and analysis	Prospective, randomized, open blinded endpoint (PROBE) design The Kaplan-Meier method was used to estimate the cumulative rates of cardiac events and other vascular events. The log-rank test was applied to assess the effect of treatment on the incidence of cardiac events. The Cox proportional hazard model was used to estimate relative risks (RR) and 95% confidence intervals (CI)
Number of participants and characteristics	N= 1650 MI: 696 (42%) Angina: 1073 (65%) Asymptomatic myocardial Ischemia: (12%) **Inclusion criteria**: Aged under 75 years who had hypertension and coronary artery disease. **Exclusion criteria**: Patients with DBP ≥120mmHg or secondary hypertension, Patients with symptomatic cerebrovascular disease, overt heart failure, atrial fibrillation, serious arrhythmias (ventricular tachycardia, ventricular fibrillation), renal dysfunction (a serum creatinine concentration of more than 176.8 mol/l), severe hepatic dysfunction, uncontrollable diabetes mellitus, and familial hypercholesterolemia. **Study level characteristics** % Male: 68.8% Mean age (SD): 64.5 (SD not reported) Ethnicity: Not reported Blood pressure at entry: 146/82 Pre-existing CVD diagnoses: MI, Angina, Asymptomatic myocardial ischemia Type 2 diabetes: Diabetes 22.5% (Type not reported) Chronic kidney disease: Not reported **Subgroup level characteristics:** baseline characteristics not reported separately for those with and without CVD Patients were enrolled at 354 Japanese hospitals specializing in the management of cardiovascular disease.

Reference	JMIC-B - Yui 2004[112]
Randomised treatments	Intervention: Nifedipine retard (N=828) Dose of 10-20 mg twice daily Comparison: ACE inhibitor (N=822) Enalapril at 5-10mg, Imidapril at 5 10mg, or lisinopril at 10 20mg, once daily Concomitant therapy: If BP reduction was unsatisfactory, an alpha blocker (doxazosin, bunazosin or prazosin) was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or beta-blockers were used concomitantly.
CVD variables	MI: 696 (42%) Angina: 1073 (65%) Asymptomatic myocardial Ischemia: (12%)
Stratification	Relative risk of cardiac events stratified by clinical characteristics: Age Sex History of MI Diabetes No formal analysis of the interaction between treatment and CVD history
Outcomes and effect sizes	Relative risk CCB vs ACE inhibitor adjusted for sex, age, history of myocardial infarction and angina pectoris using the Cox proportional hazard model. **Overall incidence of cardiac events,** History of MI: 0.91 (0.63-1.51) No history of MI: 1.26 (0.85-1.87) **Hospitalization for angina pectoris** History of MI: 0.42 (0.22-0.80) No history of MI: 1.29 (0.76-2.19) CCB better if history of MI (58% risk reduction vs ACEI)

Reference	JMIC-B - Yui 2004[112]
Comments	High attrition bias (withdrawals similar to or greater than event rate). Post-hoc subgroup analysis of RCT adjusted for sex, age, history of myocardial infarction and angina pectoris, but unclear how outcomes were selected. No indirectness noted

Reference	SHEP - Vaccarino 2001[106]
Study type and analysis	Randomized, double blind, placebo controlled clinical trial. Multivariate Cox regression model used for treatment comparisons.
Number of participants and characteristics	N= 2323 N with history of MI = 116 N with history of stroke = 30 Inclusion criteria: Age >60 years, Systolic BP >160 mmHg, Diastolic BP <90mmHg Exclusion criteria: Systolic BP >220 mmHg, recent major illness (e.g. MI) within past 6 months, stroke with residual effects **Study level characteristics** % Male: 43% Mean age (SD): 72 (SD not reported) Ethnicity: White (86%), Non-white (14%) Blood pressure at entry: mean 170/77 Pre-existing CVD diagnoses: Stroke: 1.3%, MI: 4.9% Type 2 diabetes: 10% diabetes (type not reported) Chronic kidney disease: not reported **Subgroup level characteristics**: baseline characteristics not reported separately for those with and without CVD Population source: mass mailing and community screening from 16 clinical centres
Randomised treatments	**Intervention**: Chlorthalidone (Thiazide like Diuretic) 12.5 mg Step 1: increased to 25mg, Step 2: increased to 50mg, In addition, Atenolol or reserpine if necessary N =2309

Reference	SHEP - Vaccarino 2001[106]
	Comparison: Placebo, N =2323
CVD history (subgroups reported)	History of MI or history of stroke
Confounders	In the analysis of treatment vs placebo: History of MI, Stroke, Diabetes Heart rate Total cholesterol ECG abnormalities Cigarette smoking No formal analysis of the interaction between treatment and CVD history
Outcomes and effect sizes	Proportion with events with and without prior stroke or MI Placebo CHD HF Stroke No MI history (n=2207) 125 (5.7%) 90 (4.1%) 153 (6.9%) MI history (n=116) 9 (7.7%) 13 (11.2%) 6 (5.2%) No stroke history (n=2293): 133 (5.8%) 100 (4.4) 154 (6.7) Stroke history (n=30): 1 (3.3%) 3 (10.0) 5 (16.7) Thiazide CHD HF Stroke No MI history (n=2196) 94 (4.3%) 50 (2.3%) 98 (4.3%)

Reference	SHEP - Vaccarino 2001[106]
	MI history (n=113) 6 (5.3%) 4 (3.5%) 4 (3.5%) No stroke history (n=2274): 98 (4.3%) 53 (2.3) 98 (4.3) Stroke history (n=35): 2 (5.8%) 1 (2.9) 4 (11.4) Interaction not reported
Comments	High attrition bias (withdrawals) and high proportion of those in placebo group received active treatment. Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status. No indirectness noted

A.2.2 Evidence tables from original guideline documents

The evidence tables in this section present data from the same studies as section A.2.1. They are included here as originally presented in the previous guideline versions to provide additional studies details, such as baseline characteristics and factors relevant to risk of bias assessment.

Table 36: Studies with data allowing interaction analysis (evidence tables from original guideline documents)

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
ALLHAT	I1: CCB amlodipine 2.5–10 mg/day I2: ACEi lisinopril 10–40 mg/day I3: Diuretic chlorthalidone 12.5–25 mg/day Step 2: atenolol 25–100 mg/day, reserpine 0.05–0.2 mg/day or clonidine 0.2–0.6 mg/day added and step 3 hydralazine 50–200 mg/day added 2. <140/90	USA, Canada, Puerto Rico and US Virgin Islands. Adults (≥55) with currently treated (90%) or untreated (10%) essential hypertension (BP <180/110), and at least one risk factor for CHD. Exclusion criteria symptomatic heart failure, LV ejection fraction <30%, or requiring more than 2 antihypertensive drugs for control of BP	1. participant – yes provider – yes assessor – yes 2. adequate 3. adequate 4. 42,418 5. 4.9 years	1. yes 2. 66.9 3. 53.2% 4. 59.7%	1. 146.3/84.0 I1: 146.2/83.9 I2: 146.4/84.1 I3: 146.2/84.0 2. 50.3 3. 36.2%	1. I1: 1,256/8,790 (13.9%) I2: 1,314/8,778 (14.5%) I3: 2,203/14,836 (14.4%) 2. I1: 1,466/8,790 (47.7%) I2: 1,505/8,778 (49.1%) I3: 2,451/14,836 (50.5%) 3. I1: 377/8,790 (20.8%) I2: 457/8,778 (25.0%) I3: 675/14,836 (21.0%) 4. I1: 2,432/8,790 (27.7%) I2: 2,514/8,778 (28.6%) I3: 3,941/14,836 (26.6%) 5. I1: 134.7(14.9)/74.6(9.9), 3,195 −11.5(SD)/−9.3(SD)	1. I1: 2,308/9,048 (25.5%) 2.0% adverse effects I2: 2,713/9,054 (30.0%) 2.9% adverse effects I3: 4,076/15,255 (26.7%) 1.8% adverse effects 2. I1: 258/9,048 (2.8%) I2: 276/9,054 (3.0%) I3: 419/15,255 (2.7%) 3.

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
						I2: 135.9(17.9)/75.4(10.7), 2,963 −10.5(SD)/−8.7(SD) I3: 133.9(15.2)/75.4(9.8), 5,301 −12.3(SD)/−8.6(SD)	I1: 60.5% I2: 57.0% I3: 59.3% 4. I1: 2,118/9,048 (66.3%) I2: 1,813/9,054 (61.2%) I3: 3,615/15,255 (68.2%)
ALLHAT – Black subgroup	1. I1: CCB amlodipine 2.5–10 mg/day I2: ACEi lisinopril 10–40 mg/day. I3: Diuretic chlorthalidone 12.5–25 mg/day Step 2: atenolol	Black patients enrolled in ALLHAT trial	1. participant – yes provider – yes assessor – yes 2. adequate 3. adequate 4. 11,792 black patients 5. 4.9 years (all patients)	1. good 2. 66 years 3. 45% 4. 0%	1. 146/85 2. 45% 3. 46%	1. p=0.66 (I1 vs I3); p=0.30 (I2 vs I3) I1: 481/3213 I2: 520/3210 I3: 821/53692.p=0.95 (I1 vs I3); p=0.24 (I2 vs I3) I1: 243/3213 I2: 260/3210	1. I1: 446/3213 I2: 678/3210 I3: 784/5369 2. I1: 115/3210 I2: 112/3213 I3: 186/5369 3. NR

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	25–100 mg/day, reserpine 0.05–0.2 mg/day or clonidine 0.2–0.6 mg/day added Step 3: Hydralazine 50–200 mg/day 2. SBP/DBP <140/90					I3: 400/53693. p=0.49 (I1 vs I3); p<0.001 (I2 vs I3) I1: 145/3213 I2: 212/3210 I3: 257/53694. p=0.24 (I1 vs I3); p<0.001 (I2 vs I3) I1: 767/3213 I2: 836/3210 I3: 1211/5369 5. At 4 years: I1: 137/78 I2: 138/79 I3: 135/78	4. At 4 years: I1: 60% I2: 54% I3: 63%
ASCOT	I1: CCB amlodipine <10 mg/day, with ACEi perindopril as required I2: BB atenolol <100 mg/day, with bendroflumethiazide	Patients >40 years old in Northern Europe with hypertension and at least one CV risk factor (LVH or other cardiac abnormality, stroke, diabetes, male, age >55, peripheral vascular disease, smoker,	1. open end-point 2. adequate 3. NR 4. 19,257 randomised 4. NR	1. good 2. 63.0 years 3. 77% 4. 95%	1. I1: 164/95 I2: 164/95 2. I1: LVH: 22% I2: LVH: 22%	1. I1: 738/9639 I2: 820/9618 2. Inc. silent MI I1: 429/9639 I2: 474/9618 Excluding silent MI	1. (Serious adverse events) I1: 162/9639 I2: 254/9618 2. I1: 121/9639

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	and potassium as required Step 2: alpha-blocker doxazosin GITS <8mg/day. With diabetes: SBP/DBP <130/80 Without diabetes: SBP/DBP <140/90	microalbuminuria/proteinuria, elevated cholesterol or familial CHD)	5. 5.5 years (median)		3. I1: 2567/9639 (27%) I2: 2578/9618 (27%) 4. I1: 567/7072 I2: 799/7040 (6% vs 8%)	I1: 390/9639 I2: 444/9618 3. I1: 327/9639 I2: 422/9618 4. Coronary events: I1: 753/9639 I2: 852/9618 5. 137/79	I2: 171/9618 3. I1: 15% I2: 9% 4. NR
INVEST	1. I1: Verapamil sustained release, CCB 240 mg/day (+ trandolapril (ACE) 2 mg/d for patients with diabetes, renal impairment or heart failure) I2: Atenolol, BB 50 mg/day (+ trandolapril (ACE) 2	International. Adults (50 years >) with coronary artery disease and treated essential hypertension. Excluded if treated with BB within 2 weeks randomisation or in previous 12 months for MI	1. subject – no provider – no assessor – yes 2. adequate) 3. adequate 4. 22,576 5. 2.7 years	1. yes 2. 66.1 3. 47.9% 4. 48.4%	1. 150.9/87.1 I1: 150.8/87.2 I2: 150.9/87.1 2: 100% 3: 28.4%	1. I1: 873/10,967 (8.0%) I2: 893/11,041 (8.1%) 2. (non-fatal MI only) I1: 151/10,967 (1.4%) I2: 153/11,041 (1.4%) 3. (non-fatal stroke only) I1: 131/10,967 (1.2%) I2: 148/11,041 (1.3%) 4. unclear 5.	1. I1: 1,969/11,267 17.5%) I2: 1,891/11,309 (16.7%) 2. I1: 300/11,267 (2.7%) I2: 268/11,309 (2.4%)

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	mg/day for patients with diabetes, renal impairment or heart failure) Step 2: add trandolapril 2 mg/d (I1) or hydrochlorothiazide 25 mg/d (I2); step 3: increase dose of study drug; step 4: add hydrochlorothiazide 25 mg/d (I1) or trandolapril 2 mg/d (I2); step 5: maximum tolerated dose of study drug and non-study antihypertensive drugs except BB (I1) or CCB (I2) 2. 140/90 mmHg					I1: −18.7(22.2)/−10.0(12.4), 7,842 I2: 9.0(22.6)/−10.2(12.4), 7,850	3. I1: 1,964/8,639 (22.7%) I2: 1,920/8,694 (22.1%) 4. I1: 5,625/7,842 (71.7%) I2: 5,553/7,850 (70.7%)

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	130/85 mmHg if diabetes or renal impairment						
JMIC-B	I1: CCB nifedipine retard 10–20 mg bid. I2: ACEi enalapril/imidapril 5–10 mg/day or lisinopril 10–20 mg/day. Step 2: alpha-blocker if required for hypertension; BB or nitrate for angina SBP/DBP <150/90	Japanese patients with essential hypertension and comorbid coronary artery disease without acute MI, unstable angina, renal/hepatic dysfunction, uncontrolled diabetes, cerebrovascular disease or overt heart failure	1. open end-point 2. adequate 3. adequate 4. 1,650 randomised 4. 3 years 5. 35.7 months	1. good 2. 65.6 years 3. 69% 4. NR	1. treated: 145/81 untreated: 161.5/92 2. NR 3. 23% 4. NR	1. I1: 12/828 I2: 15/822 2. I1: 16/828 I2: 13/822 3. I1: 16/828 I2: 16/822 4. I1: 116/828 I2: 106/822 5. I1: 136/77 I2: 138/79	1. adverse events I1: 12.9% I2: 17.3% 2. I1: 107/828 I2: 114/822 3. NR 4. NR
SHEP	I. Chlorthalidone 12.5–25 mg/day C: Placebo Step 2: atenolol 25–50 mg/day or reserpine 0.05–0.10 mg/day added in I;	USA. Adults (≥60) with isolated systolic hypertension (SBP 160–219 and DBP <90), 33% currently treated. Exclusion criteria renal dysfunction	1. participant – yes provider – yes assessor – yes 2. unclear 3. adequate 4. 4,736	1. yes 2. 71.6 3. 43% 4. 86.1%	1. 170.3/76.6 I: 170.5/76.7 C: 170.1/76.4 2. 6.3%	1. I: 213/2,365 (9.0%) C: 242/2,371 (10.2%) 2. I: 140/2,365/ (5.9%) C: 184/2371 (7.8%) 3.	1. I: 448/1221 (36.7%) 3% received known active therapy as BP was too high 13% stopped

Trial	1. Comparison 2. Target blood pressure	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow-up	1. Baseline comparability 2. Age 3. Male % 4. White %	1. Blood pressure 2. CVD % 3. Diabetes % 4. New diabetes	1. Total mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	matching stepped care in C 2. SBP <160 baseline SBP ? 180 and reduction >20 if baseline SBP 160–179		5. 4.5 years		3. 10.1%	I: 103/2,365 (4.4%) C: 159/2,371 (6.7%) 4. I: 199/2,365 (8.4%) C: 289/2,371 (12.2%) 2 and 4 are number of events, 1 and 3 are number of patients 5. I: 144.0(19.3)/67.7(10.2), 773 –26.5(SD)/–9.0(SD) C: 155.1(20.9)/71.1(12.8), 738 –15(SD)/–5.3(SD)	medication because of side effects C: 570/1308 (43.6%) 44% received known active therapy as BP was too high 2. unclear 3. I: 30% C: 54% 4. I: 65–72% C: 32–40%

Table 37: Studies with data allowing interaction analysis (evidence tables from original 2011 guideline documents)

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>ONTARGET

S. Yusuf, K. K. Teo, J. Pogue, L. Dyal, I. Copland, H. Schumacher, G. Dagenais, P. Sleight, and C. Anderson. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358 (15):1547-1559, 2008.

Ref ID: 41</td>
<td>RCT

Multi-centre, international trial (733 centres, 40 countries)

Randomised (permuted blocks, stratified by site)
No explicit ‘washout’ but had run-in period
Double blind
Allocation concealment
Sample size calculation (1o outcome)
ITT analysis
Unclear dropouts: this is important in such a large and long trial</td>
<td>Total N: 25,620

Drop-outs (don’t complete the study) = different to drug withdrawal as these may still be measured and included in ITT): Unclear / not mentioned

Proportion of pts on full dose of ACE at 2 years: ACE group 82%, ACE+AR</td>
<td>Inclusion criteria: patients with vascular disease or high-risk diabetes; patients had coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage. (HIGH RISK PATIENTS). Patients who could not tolerate ACE were assigned to ARB or placebo. NOTE: 69% of patients had hypertension.

Exclusion criteria: People entering the run-in period were excluded from the study for: poor compliance (3.9%), withdrew (1.7%), had symptomatic HT (2.1%), elevated potassium (0.8%), elevated creatinine (0.2%), other reasons (3%) or died (0.1%).

<table>
<tr><td>Mean baseline</td><td>ARB (n=8542)</td><td>ACE (n=8576)</td><td>ACE + ARB (n=8502)</td></tr>
<tr><td>Mean age – years (SD)</td><td>66.4 (7.1)</td><td>66.4 (7.2)</td><td>66.5 (7.3)</td></tr>
<tr><td>Gender M/F</td><td>74% / 26%</td><td>73% / 27%</td><td>73% / 27%</td></tr>
</table>
</td>
<td>N=8542

ARB

telmisartan
80 mg/day

N=8576

ACE

ramipril
5 mg/day for 2 weeks then increased to 10 mg/day

MEDICATION at end of study:

ARB group: ARB 86%, ACE 6.4%</td>
<td>N=8502

ARB + ACE

Telmisartan + ramipril

Doses as for other groups (including increase at 2 weeks of ACE)

NOTE: one step dose adjustment protocol for ACE but not different steps of different drugs; note most pts = coronary artery disease and HT; most pts previously</td>
<td>Median follow up 56 months

Pts followed until a primary event occurred or until end of study.</td>
<td>1o outcome: composite of Death from CV causes, MI, stroke or hospitalisation for HF.

2o and other outcomes: new HF; diabetes mellitus; AF; revasculari sation procedures; all cause death.</td>
<td>Boehringer Ingelheim; Heart and Stroke Foundation of Ontario and Canadian Institutes of Health Research</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Trial was designed to test non-inferiority or superiority of the ARB.	B group 75% Proportion of pts on full dose of ARB at 2 years: ARB group 89%, ACE+ARB group 84%	Ethnicity African European	2.5% 72.7%	2.4% 73.1%	2.4% 73.2 %	ACE group: ACE 85%, ARB 3.3% ARB + ACE group: ACE+ARB 74%, ACE 6%, ARB 6%,	taken a-HT drugs esp. BB			
			BMI (SD)	28 (4.6)	28 (4.5)	28 (4.5)					
			BP - sys/dia	142/82	142/82	142/82					
			Previous HT treatment								
			BB	57%	57%	57%					
			Diuretic	28%	29%	28%					
			CCB	33%	33%	34%					
			Previous diseases								
			Diabetes	38%	37%	38%					
			Hypertension	69%	69%	69%					
			Previous MI	49%	48%	49%					
			Previous stroke or TIA	21%	21%	21%					
			Coronary	75%	74%	75%					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			artery disease The 3 groups were similar for baseline characteristics					

Effect Size

Outcomes (intention to treat population)

Pts in the ARB and ACE+ARB groups continued to have slightly lower BP levels throughout the study (mean reduction 0.9/0.6 and 2.4/1.4 mm Hg respectively) compared to the ACE group (mean reduction not given; assume was same as at 6 weeks?).

Pts discontinued study drug due to cough: ARB (4.2%) and ACE (1.1%)

Outcome	ARB (N=8542)	ACE (N=8576)	ARB + ACE (N=8502)	ARB vs ACE RR (95% CI) reported in paper	Combi vs ACE RR (95% CI) reported in paper	Combi vs ARB RR (95% CI) calculated from data
1o outcome: composite of Death from CV causes, MI, stroke or hospitalisation for HF	1423	1412	1386	1.01 (0.94, 1.09) - NS	0.99 (0.92, 1.07) - NS	-
Main 2o outcome: composite of Death from CV causes, MI, stroke	1190	1210	1200	0.99 (0.91, 1.07) - NS	1.00 (0.93, 1.09) - NS	-
Mortality (all cause), n	989	1014	1065	0.98 (0.90, 1.07) – NS p=0.62	1.07 (0.98, 1.16) - NS	1.08 (1.00, 1.17) - NS
MI (fatal and non-fatal), n	440	413	438	1.07 (0.94, 1.22) – NS p=0.31	1.08 (0.94, 1.23) - NS	1.00 (0.88, 1.14) - NS
Stroke (fatal and non-fatal), n	369	405	373	0.91 (0.79, 1.05) – NS p=0.21	0.93 (0.81, 1.07) - NS	1.02 (0.88, 1.17) – NS

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Outcome	ARB (N=8542)	ACE (N=8576)	ARB + ACE (N=8502)	ARB vs ACE RR (95% CI) reported in paper	Combi vs ACE RR (95% CI) reported in paper	Combi vs ARB RR (95% CI) calculated from data
Hospitalisation for angina, n	954	925	952	1.04 (0.95, 1.14) – NS p=0.42	1.04 (0.97, 1.14) - NS	1.00 (0.92, 1.09) - NS
Coronary revascularisation procedure, n	1290	1269	1303	1.03 (0.95, 1.11) – NS p=0.58	1.04 (0.97, 1.13) - NS	1.01 (0.95, 1.09) - NS
New onset diabetes, n	399 / 5294	366 / 5427	323	1.12 (0.97, 1.29) – NS p=0.11	0.91 (0.78, 1.06) - NS	0.81 (0.70, 0.94) – SS (COMBI)
Heart failure, n	537	514	478	1.05 (0.93, 1.19) – NS p=0.42	0.94 (0.83, 1.07) - NS	0.89 (0.79, 1.00) – NS
Study drug withdrawal,* n	1796 (21%)	2029 (24%)	1929 (23%)	0.89 (0.84, 0.94) – SS (ARB) Calculated from data P<0.0001	-	-
Blood pressure (mean reduction at 6 wks; mmHg)	S: 7.4 D: 5.0	S: 6.4 D: 4.3	S: 9.8 D: 6.3	-	-	-
Blood pressure (mean reduction throughout study; mmHg)	S: 0.9 D: 0.6	- -	S: 2.4 D: 1.4	-	-	-

Incidence of primary outcome in ramipril group
CVD (n=15,672): 16.8%
No CVD (n=1486): 13.1%

- p for interaction 0.79

*NOTE: after the run-in period, patients who had poor compliance were excluded from the study (i.e.. did not enter into the randomisation of treatment - ACE vs ARB); Compared to the ARB group, more patients in the ACE or ACE + ARB groups discontinued treatment because of cough or angioedema.

A.3 Studies with exclusively CVD populations

The evidence tables in this section are taken from previous versions of the guideline. They are restricted to those studies with inclusion criteria limited to those with a CVD diagnosis.

Table 38: Studies with exclusively CVD populations (evidence tables from original 2004/2006 guideline documents)

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
HSCSG	I: methychlothiazide 10mg/day and deserpidine 1 mg/day C: placebo 2. not reported	USA. Adults (< 75) with essential hypertension (BP 140–220/90–115) and a CVA and/or TIA < 1 year.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 452 5. 2.1 years	1. unclear 2. 59 3. 58.6% 4. 19.5%	1. 167/100 I: 167/100 C: 167/100 2: 100% 3: unclear	1. I: 26/223 (11.7%) C: 24/215 (11.2%) 2. I: 5/223 (2.2%) C: 7/215 (3.3%) 3. I: 37/223 (15.9%) C: 42/215 (19.2%) 4. I: 42/223 (18.8%) C: 49/215 (22.8%) 5. I: 137(SD)/84(SD),44 −30(18.7)/−16(9.3) C: 167(SD)/98(SD),37 0(20.1)/−2(11.4)	1. I: 83/233 (35.6%) C: 84/219 (38.4%) 2. I: 10/233 (4.3%) C: 4/219 (1.8%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
PATS	I: indapamide 2.5 mg/day C: placebo 2. not reported	China. Adults with a history of CVA or TIA (> 4 weeks) irrespective of BP (BP <140/90 in 16% and BP ≥160/95 in 57%). Exclusion criteria secondary hypertension, type 1 diabetes or renal disease.	1. participant – yes provider – yes assessor – unclear 2. unclear 3. inadequate 4. 5,665 5. 2 years	1. yes 2. 60 3. 72% 4. not reported	1. 153.8/92.8 I: 154.0/93.0 C: 153.5/92.6 2: 100% 3: excl. type I diabetes	1. I: 146/2,841 (5.1%) C: 158/2,824 (5.6%) 2. I: 25/2,841 C: 21/2,824 3. I: 159/2,841 (5.6%) C: 217/2,824 (7.7%) 4. unclear I: 194/2,841 C: 247/2,824 5. I: 142.6(16.9)/85.7(8.7), n/a −11.4(SD)/−7.3(SD) C: 148.8(19.1)/88.6(10.1), n/a -−4.7(SD)/−4.0(SD)	1. I: 308/2,841 (10.8%) 3.4% adverse effects C: 308/2,824 (10.9%) 3.6% adverse effects 2. I: 0/2,841 (0)%) C: 0/2,824 (0%) 3. not applicable 4. not applicable
DUTCH TIA	1. I: atenolol 50 mg/d β-blocker C: placebo 30 mg/day aspirin was taken	The Netherlands. Adults with a TIA or non-disabling stroke < 3 months. Exclusion	1. subject – adequate provider – adequate assessor – adequate	1. unclear 2. not reported 3. 64% 4. not reported	1. 157.5/91.0 I: 158/91 C: 157/91 2: 72%	1. I: 64/732 (13.3%) C: 58/741 (12.8%) 2. I: 45/732 (6.1%) C: 40/741 (5.4%)	1. I: 350/732 (48%) C: 316/741 (43%) 2. unclear 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	at baseline by 48% subjects in both groups 2. not reported	criteria: cerebral ischaemia, patients with contra-indications for β-blocker treatment or strict indication for β-blocker treatment Indirect: only 29% had hypertension	2. adequate 3. inadequate (telephone) 4. 1,473 5. 32 months		3: 5.0%	3. I: 52/732 (7.1%) C: 62/741 (8.4%) 4. unclear 5. I: 148(SD)/86(SD) −10(SD)/−5(SD) C: 150(SD)/87(SD) −8(SD)/−4(SD)	
TEST	1. I: atenolol 50 mg/d β-blocker C: placebo 2. not reported	Sweden. Adults > 40 years with a TIA or non-disabling stroke <3 wks ago and hypertension >140/80 mm Hg. Exclusion criteria: CHD, life threatening disorders (subarachnoid haemorrhage, heart failure), patients with contra-indications for β-	1. subject – adequate provider – adequate assessor– unclear 2. adequate 3. unclear 4. 720 5. 2.3 yrs	1. yes 2. 70.4 3. 60.1% 4. unclear	1. 161.0/88.5 I: 161/88 C: 161/89 2: 90% 3: 12.5%	1. I: 51/372 (13.7%) C: 60/348 (17.2%) 2. I: 26/372 (7.0%) C: 29/348 (8.3%) 3. unclear I: 74/372 (19.9%) C: 69/348 (19.8%) 4. unclear I: /372 C: /348 5. I: 157(SD)/85(SD), 372	1. I: 114/372 (31%) C: 95/348 (27%) 2. I: 0/372 (0%) C: 0/348 (0%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
		blocker treatment				−4(SD)/−3(SD) C: 161(SD)/89(SD), 358 0(SD)/0(SD)	
PROGRESS	I: ACE-inhibitor perindopril 4 mg/day, combined with diuretic indapamide 2.5 mg/day (2.0 mg/day in Japan) if the treating physician deemed this appropriate C: placebo 2. none	Australia, New Zealand, China, Japan, Western Europe. Adults with a history of CVA or TIA < 5 years and with or without hypertension; Exclusion criteria no definite indication or contraindication for taking ACE-inhibitors. Indirect: only 48% had hypertension	1. participant – yes provider – yes assessor – no 2. adequate 3. unclear 4. 6,105 5. 3.9 years	1 yes 2. 64.0 3. 70.0% 4. 61.0%	1. 147/86 I: 147/86 C: 147/86 2. 100% 3. 12.5%	1. I: 306/3,049 (10.0%) C: 319/3,053 (10.4%) 2. I: 115/3,049 (3.9%) C: 154/3,053 (5.2%) 3. I: 307/3,049 (19.1%) C: 420/3,053 (26.2%) 4. Incl. "other vascular" deaths I: 458/3,049 (15%)3,049 C: 604/3,053 (19.8%)3,053 All the above are number of events. 5. I: 133(SD)/80(SD), 3049 −14(11.7)/−6(7.8) C: 142(SD)/84(SD), 3053 −5(11.7)/−2(7.8)	1. I: 1,020/3,051 (33.4%) 7.6% participants decision 2.2% cough 2.1% hypotension 2.2% heart failure C: 955/3,054 (31.3%) 8.2% participants decision 0.4% cough 0.9% hypotension 2.3% heart failure 2. I: 2/3,051 (0.07%) C: 1/3,054 (0.03%) 3. I: 1,281 (42%) C: 1,280 (42%) 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
INVEST	1. I1: verapamil sustained release, calcium-channel blocker 240 mg/d (+trandolapril (ACE) 2 mg/d for patients with diabetes, renal impairment or heart failure) I2: atenolol, β-blocker 50 mg/d (+trandolapril (ACE) 2 mg/d for patients with diabetes, renal impairment or heart failure) Step 2: add trandolapril 2 mg/d (I1) or hydrochlorothiazide 25 mg/d (I2); step 3: increase dose of study drug; step 4: add hydrochlorothiazide 25 mg/d (I1)	International. Adults (50 yrs >) with coronary artery disease and treated essential hypertension. Excluded if treated with β–blockers within 2 wks randomisation or in previous 12 months for MI	1. subject – no provider – no assessor – yes 2. adequate) 3. adequate 4. 22,576 5. 2.7 years	1. yes 2. 66.1 3. 47.9% 4. 48.4%	1. 150.9/87.1 I1: 150.8/87.2 I2: 150.9/87.1 2: 100% 3: 28.4%	1. I1: 873/10,967 (8.0%) I2: 893/11,041 (8.1%) 2. [non-fatal MI only] I1: 151/10,967 (1.4%) I2: 153/11,041 (1.4%) 3. [non-fatal stroke only] I1: 131/10,967 (1.2%) I2: 148/11,041 (1.3%) 4. unclear 5. I1: −18.7(22.2)/−10.0(12.4), 7,842 I2: 9.0(22.6)/−10.2(12.4), 7,850	1. I1: 1,969/11,267 17.5%) I2: 1,891/11,309 (16.7%) 2. I1: 300/11,267 (2.7%) I2: 268/11,309 (2.4%) 3. I1: 1,964/8,639 (22.7%) I2: 1,920/8,694 (22.1%) 4. I1: 5,625/7,842 (71.7%) I2: 5,553/7,850 (70.7%)

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes %	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
	or trandolapril 2 mg/d (I2); step 5: maximum tolerated dose of study drug and non-study anti-hypertensive drugs except β-blocker (I1) or calcium-channel blocker (I2) 2. 140/90 mmHg 130/85 mmHg if diabetes or renal impairment						

Table 39: Studies with exclusively CVD populations (evidence table from original 2011 guideline documents)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Alem M. +, P. Milia, S. Muir, K. Lees, and M. Walters. Comparison of the effects of diuretics on blood pressure and	RCT Single centre (UK) Randomisation: Block randomisation	N = 26	Inclusion criteria: Ambulant patients with first-ever ischemic stroke or transient ischemic attack (TIA) were recruited. All patients began the trial protocol between 4 and 6 weeks after stroke.	N = 13 Indapamide (IND) 2.5mg daily for 28 days	N = 13 Bendroflumethiazide (BDZ) 2.5 mg daily for 28 days	28 days end of treatment	1o outcome BP Arterial stiffness	No details

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
arterial stiffness in patients with stroke. Journal of Stroke and Cerebrovascular Diseases 17 (6):373-377, 2008. Ref ID 15972:	Allocation concealment: Central pharmacy Blinding: open labelled Sample size calculation: Yes based on augmentation index ITT analysis: No Drop outs: 3 from the Bendroflumethiazide group (1 for intercurrent viral illness and 2 for personal reasons). Multiple regression: Age, sex, SBP, DBP, Drug, Mean arterial pressure		Exclusion criteria: Patients with significant post-stroke disability, comorbidity, or contraindication to antihypertensive treatment. Baseline / IND n=13 / BDZ n=10 Male (n) / 5 / 6 Age (years) / 70.1 ± 7.0 / 69.1 ± 12.4 BMI (SD) / 24.9 ± 4.5 / 25.8 ± 4.2 Mean SBP (SD) / 144.5 ± 15.5 / 131.9 ± 24.1 Mean DBP (SD) / 78.3 ± 7.4 / 74.0 ± 10.3 NOTE: Most patients were newly diagnosed and therefore untreated but others had their antihypertensive therapy withdrawn 3 weeks before the study.	4 patients on statins. No other antihypertensive medication administered.	6 patients on statins. . No other antihypertensive medication administered.		Method of BP measurement: Mean of 3 measurements after lying supine for 30 minutes in the clinic using a Dinamap.	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			At the end of 16 weeks, 12 patients then had a further 16 weeks of combined treatment.					

Effect Size
Both IND and BDZ reduced BP to a significant degree.

No target BP defined in the study. No details on % responders.

Outcome	IND n=13	BDZ n=10
Mean SBP absolute change (SD)	18.8 ± 14.1	13.2 ± 18.8
Mean DBP absolute change (SD)	8.6 ± 6.4	5.4 ± 5.9

A.4 Information on prior antihypertensive drug use for trial participants

Table 40: Prior anti-hypertensive drug use before trial recruitment

Trial	Inclusion of those on anti-hypertensives	% on anti-hypertensives at recruitment	Antihypertensive drug classes used before recruitment
Alem, 2008[1]	Antihypertensive were withdrawn prior to entry	Not stated	Not stated
ALLHAT[56, 75, 76, 82]	Drug withdrawal procedure was not required, patients continued their anti-	90%	Not stated

Trial	Inclusion of those on anti-hypertensives	% on anti-hypertensives at recruitment	Antihypertensive drug classes used before recruitment
	hypertensives until the study drug was given.		
ANBP2[110]	Study participants went through drug withdrawal procedure	Treatment A: 62% Treatment B: 62%	Not stated
ASCOT[20, 26]	Not stated	Treatment A: 81% Treatment B: 81%	Not stated
CORD IB[97]	Excluded if receiving ACE or ARB	Unclear	45% diuretics, 42% beta blocker, 28% calcium channel blockers
De Souza 2010[28]	Anti-hypertensive treatment unchanged	100%	Diuretics: 100% ACE inhibitors/AR blockers: 94% Beta blockers: 85% Calcium channel blockers: 71% Direct vasodilators: 46% Central agonists: 23%
DUTCH-TIA[105]	No run-in period was required	Not stated	Not stated
HSCSG[32]	All anti-hypertensive medication were discontinued, and patients went through 4 weeks placebo run in period	Not stated	Not stated
HYVET[7]	2 months placebo after withdrawal of all anti-hypertensives	Intervention: 64% Placebo: 65%	Not stated
INSIGHT[14, 15]	2-4 weeks placebo run in	Not stated	Not stated
INVEST[78]	Not stated	Treatment A: 86.6% Treatment B: 86.5%	ACE inhibitor: 51.4% Centrally acting: 5.4% Calcium antagonist: 41.3% Diuretic: 37.8% alpha-blocker/other vasodilator: 8.5% Other class: 22.3%
JMIC-B[111, 112]	Not stated	Treatment A :98% Treatment B: 89%	Diuretics: 5% Beta-Blockers: 20% Alpha-Blockers: 4.3%

Trial	Inclusion of those on anti-hypertensives	% on anti-hypertensives at recruitment	Antihypertensive drug classes used before recruitment
			Calcium-channel blockers: 51% ACE inhibitors: 13.2%
LIFE[22, 60, 61]	1-2-week placebo run in	Not stated	Not stated
MIDAS[11, 17]	3–8-week placebo washout period	76%	44% diuretics, 18% beta blockers, 20% ACE inhibitors, 10% calcium antagonist
MRC[72]	Patients taking anti-hypertensives were excluded	-	None
MRC-O[70]	Patients taking anti-hypertensive were excluded	-	None
ONTARGET[113]	Run in period: 2.5 mg of ramipril once daily for 3 days, followed by 40 mg of telmisartan and 2.5 mg of ramipril once daily for 7 days and then 5 mg of ramipril plus 40 mg of telmisartan for 11 to 18 days.	57% BB 28% diuretics 33% CCB	Beta blockers Calcium channel blocker Diuretic
PATS[77]	Placebo run in period	Not stated	Not stated
PROGRESS[64]	4-week pre-randomisation run-in period of open-label perindopril	Intervention 50% Placebo 51% Combination 50% Single 51%	Not stated
SCOPE [46, 62]	Any previous anti-hypertensive medication was standardized to hydrochlorothiazide 12.5mg	Intervention: 52.4 Control 53%	Not stated
SHEP[79, 85, 89, 106]	Included after drug withdrawal procedure.	Intervention 33.0% Placebo 33.5%	Not stated
SHEP-P[48, 80, 81]	Went through drug withdrawal procedure	Intervention: 46% Placebo: 50%	Not stated
STOP-H2[24, 44, 45, 59]	Placebo wash out period	Not stated	Not stated
SYST-EUR[3, 19, 40, 98-100]	Included after drug withdrawal procedure	Intervention: 46%, Placebo: 47%	Not stated

Trial	Inclusion of those on anti-hypertensives	% on anti-hypertensives at recruitment	Antihypertensive drug classes used before recruitment
TEST [37]	Not stated	Not stated	Not stated
THAI elderly[104]	Anti-hypertensives were withdrawn two weeks prior to study	Not stated	Not stated
VALUE[52]	Wash out period was not required: patients already receiving antihypertensive treatment discontinued taking previous drugs and began randomised treatment	Treatment A: 92.7% Treatment B: 92%	Ace inhibitor: 41.3% Angiotensin receptor blocker: 10.6% Alpha- blocker: 6.8% Beta- blocker: 33.2% Calcium channel antagonist: 40.9% Diuretics as monotherapy: 26.8% Fixed dose diuretic combination: 8.7%
VHAS[93, 116]	3-week placebo run in	Not stated	Not stated

Appendix B Forest plots

B.1 CVD history subgroup analyses: Thiazide-like diuretic versus placebo

B.1.1 Presence or absence of history of myocardial infarction (MI)

Figure 4: Coronary heart disease in those with and without MI history

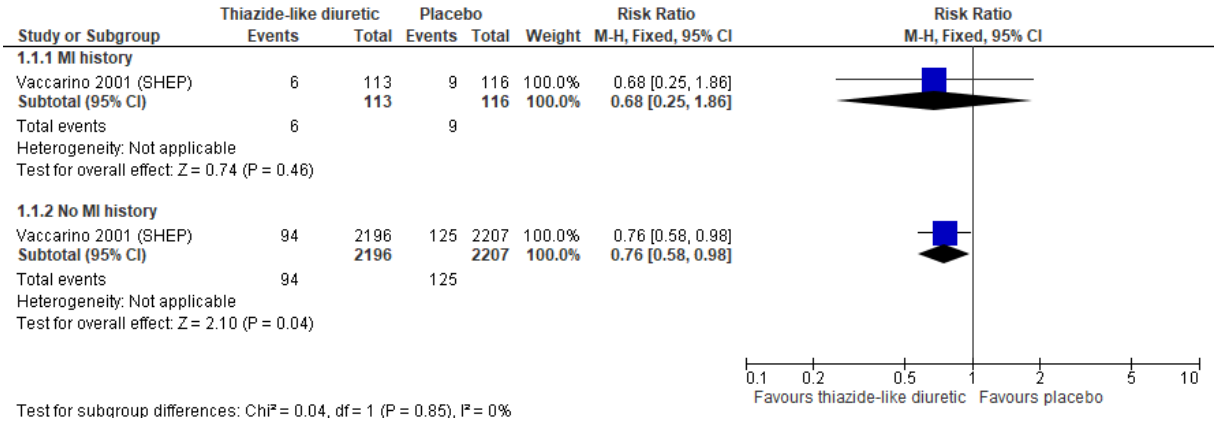


Figure 5: Heart failure in those with and without MI history

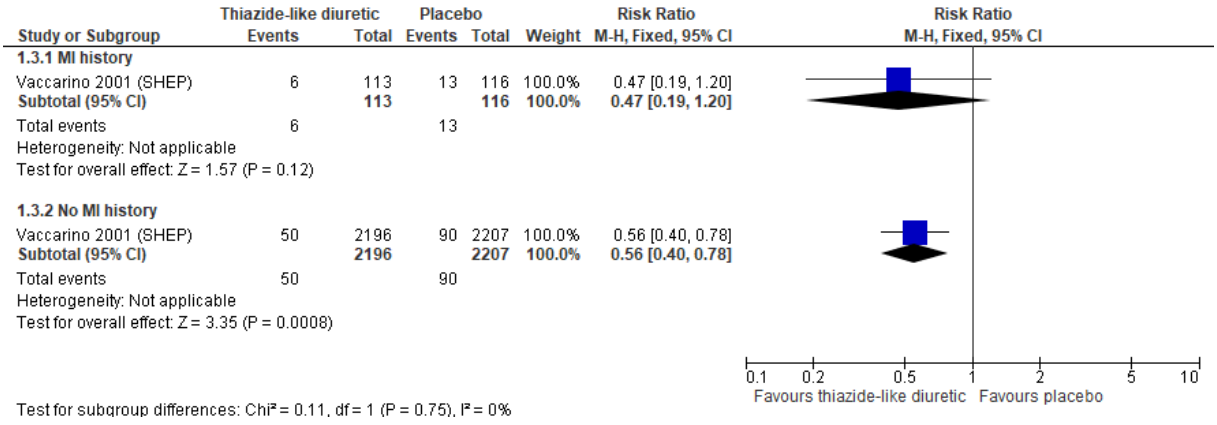
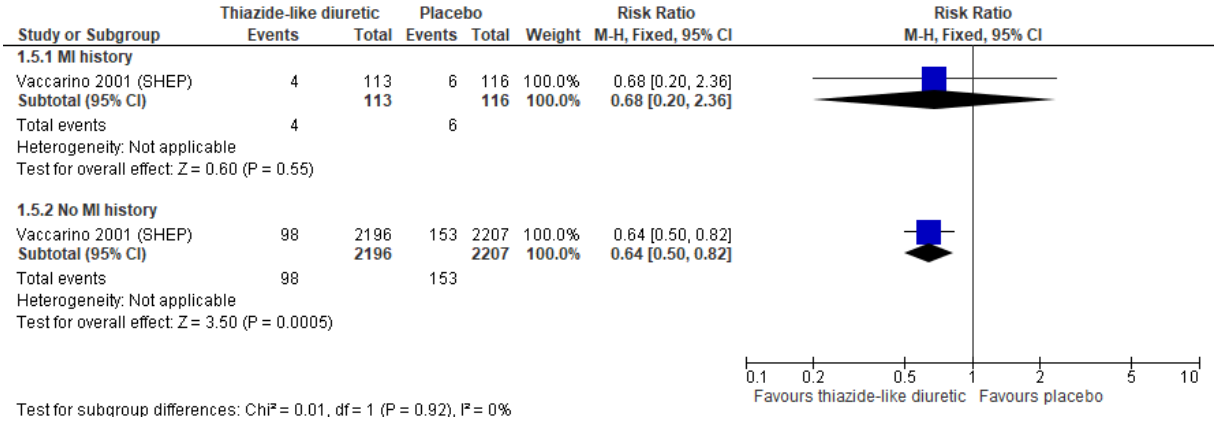


Figure 6: Stroke in those with and without MI history



B.1.2 Presence or absence of history of stroke

Figure 7: Coronary heart disease in those with and without stroke history

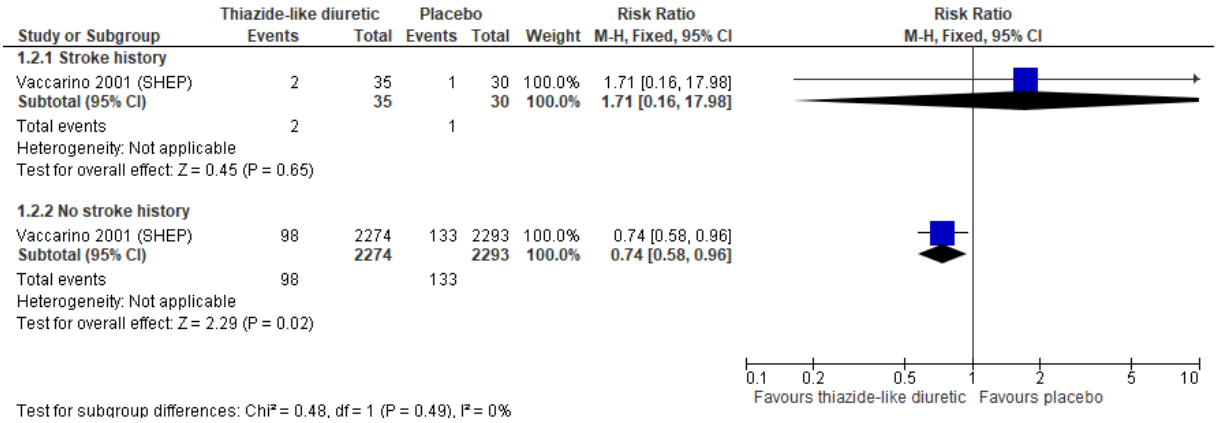


Figure 8: Heart failure in those with and without stroke history

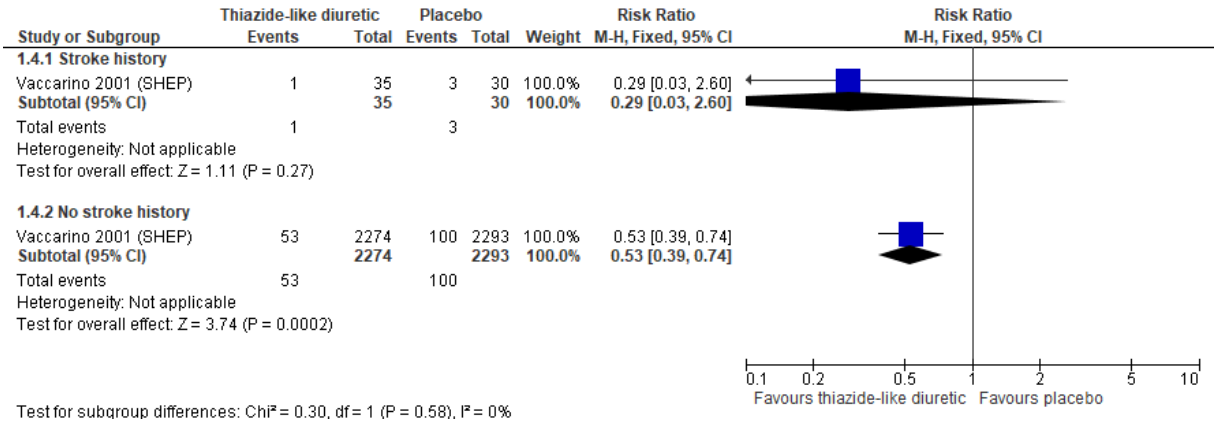
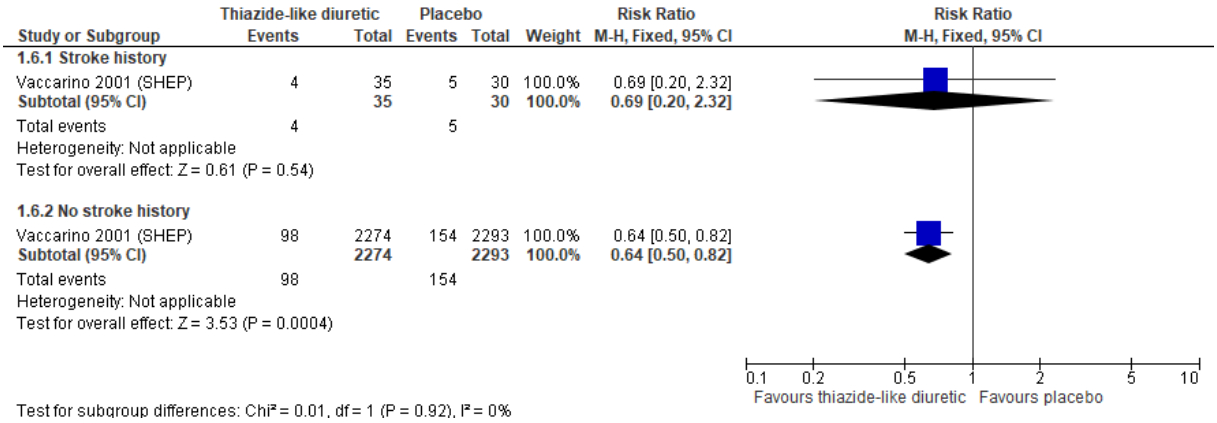


Figure 9: Stroke in those with and without stroke history



B.2 CVD history subgroup analyses: calcium channel blocker versus ACE inhibitor

B.2.1 Presence or absence of history of coronary heart disease (CHD)

Figure 10: All-cause mortality in those with and without CHD history

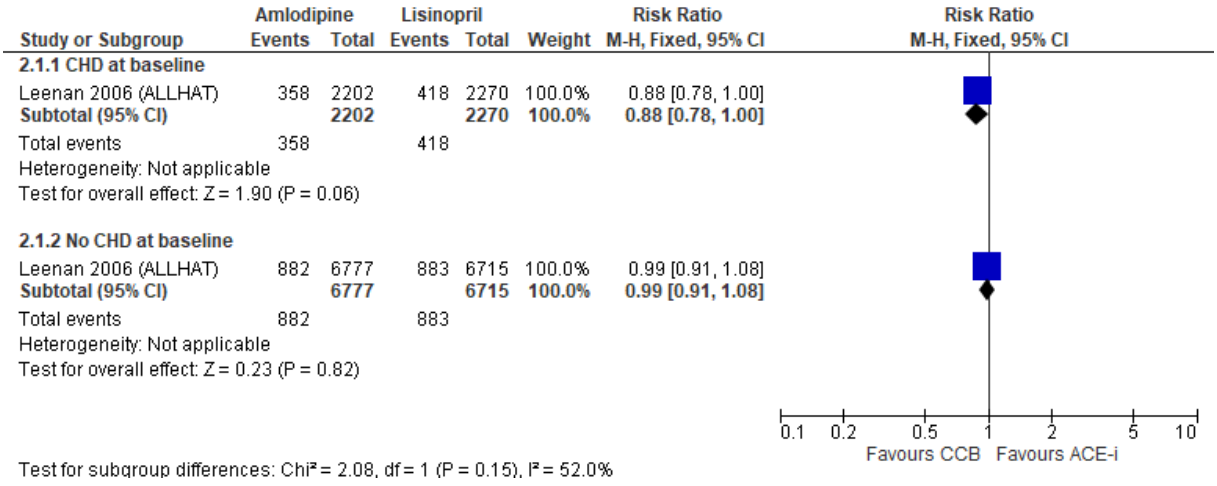


Figure 11: Coronary heart disease events in those with and without CHD history

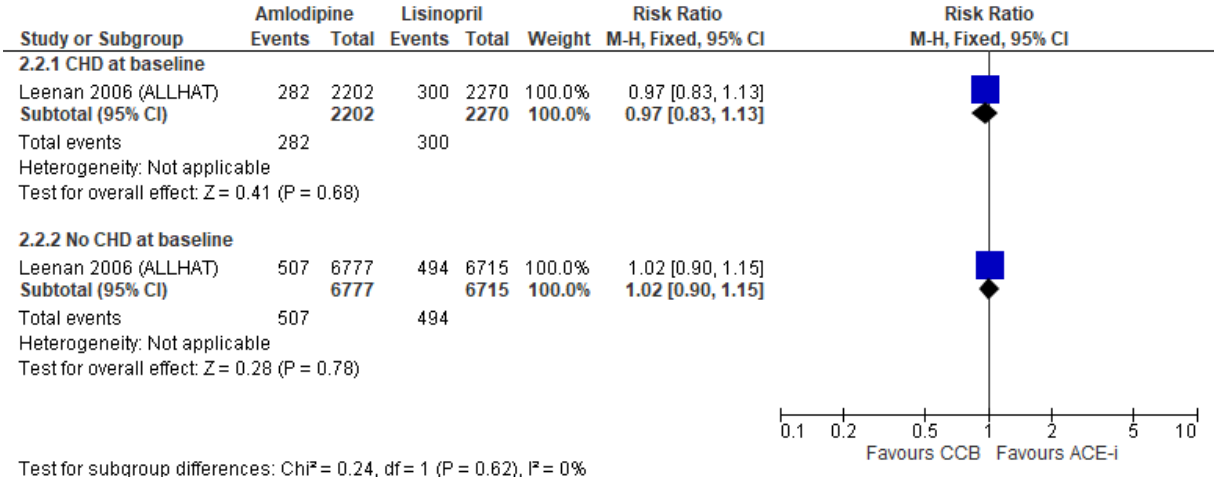


Figure 12: Stroke (fatal or non-fatal) in those with and without CHD history

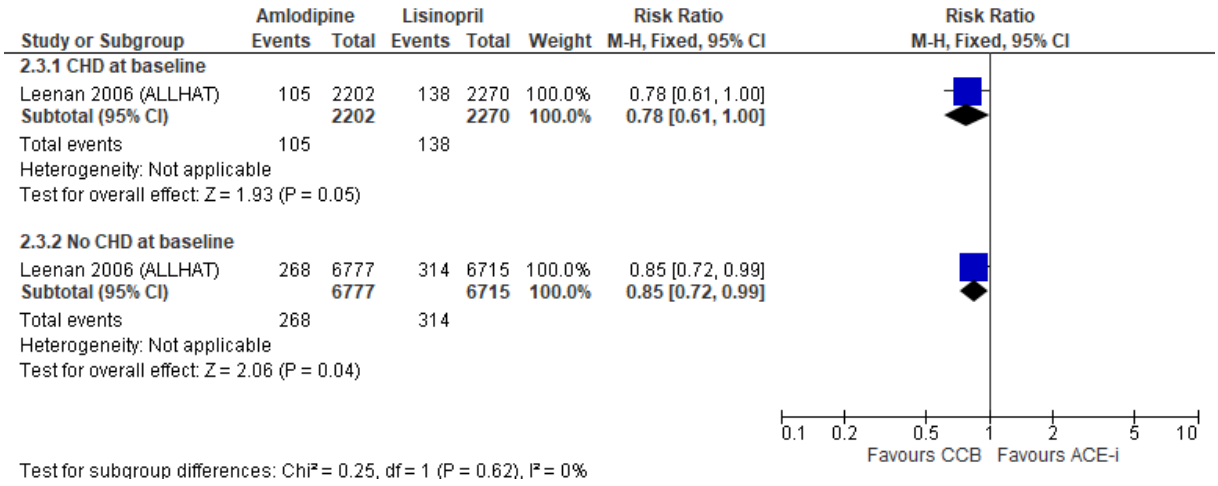


Figure 13: Heart failure in those with and without CHD history

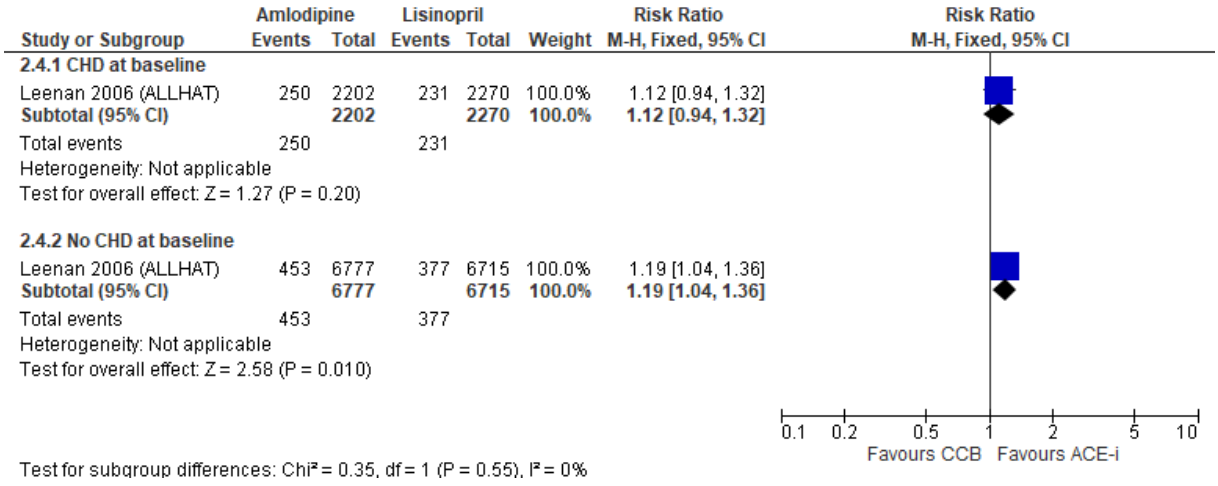


Figure 14: Angina in those with and without CHD history

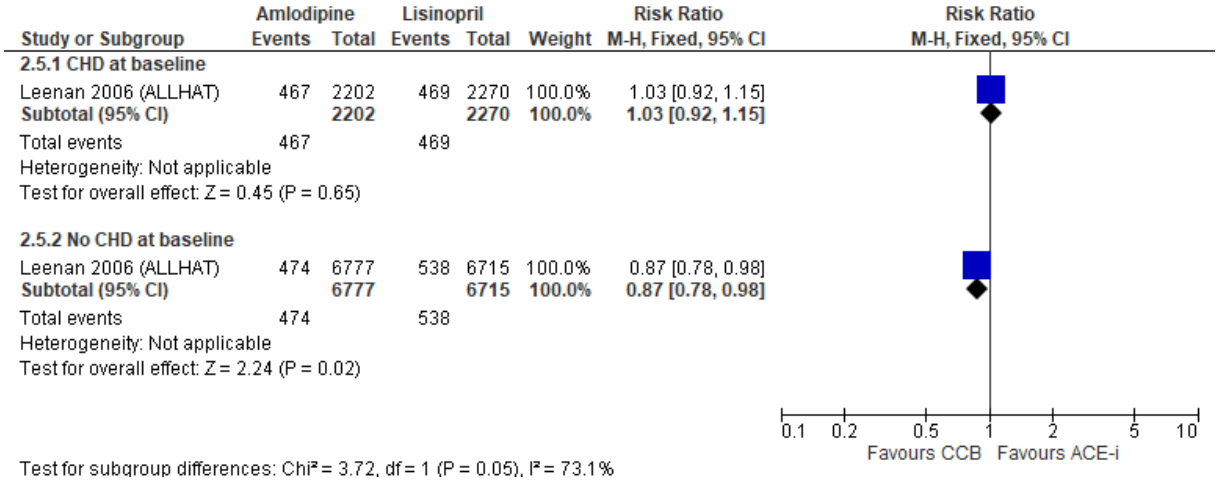


Figure 15: Coronary revascularisation in those with and without CHD history

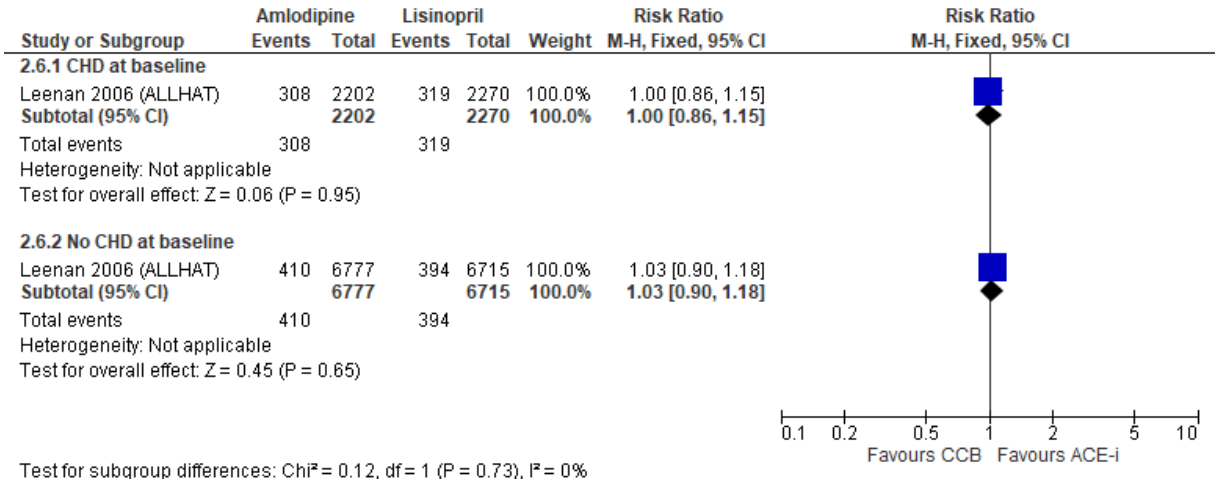
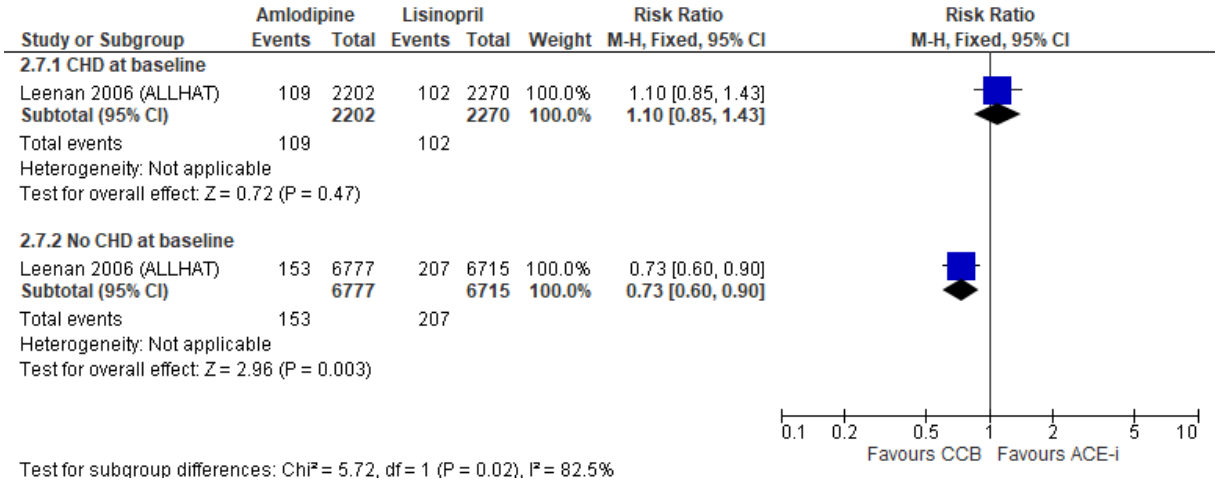


Figure 16: Peripheral arterial disease in those with and without CHD history



B.2.2 Presence or absence of history of myocardial infarction (MI)

Figure 17: Cardiac events in those with and without MI history

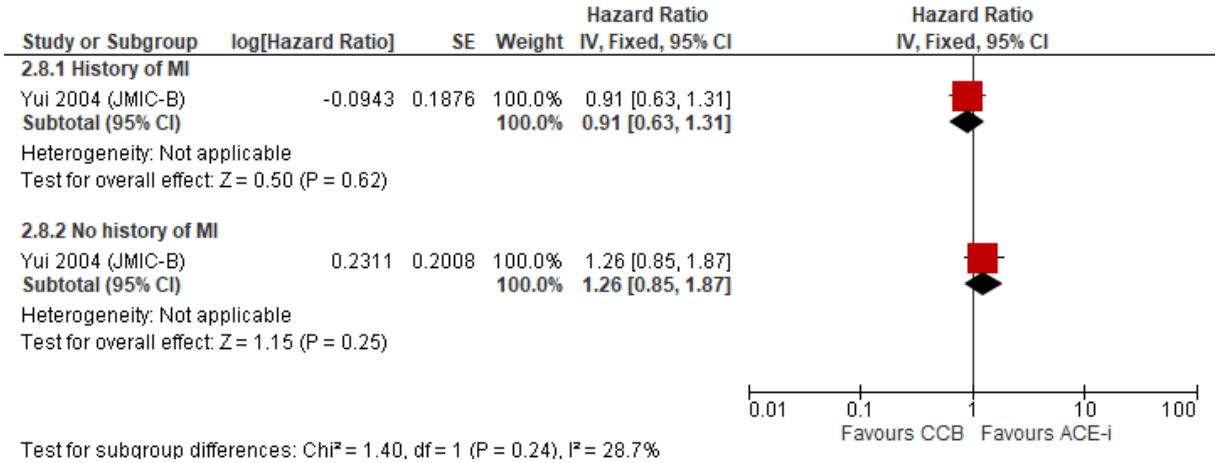
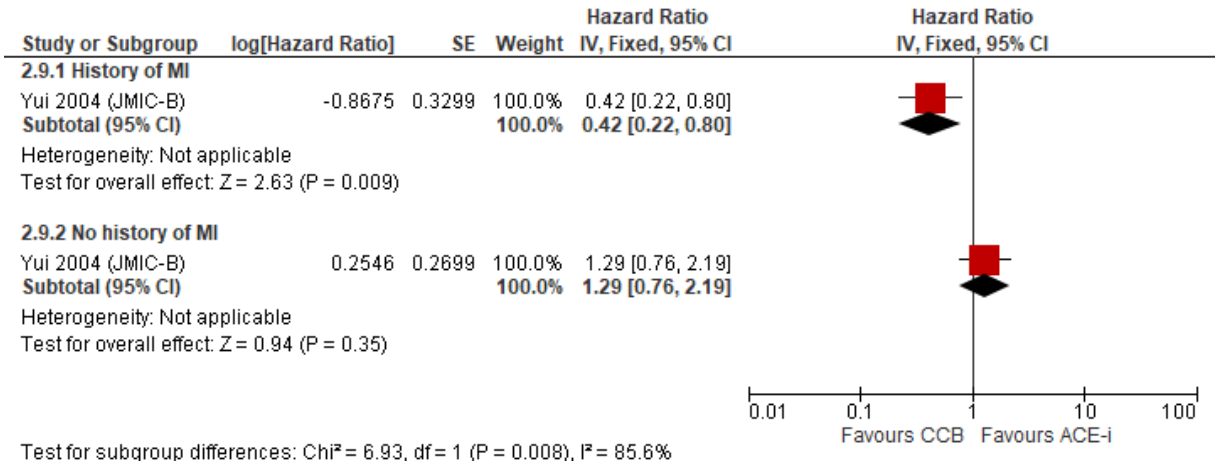


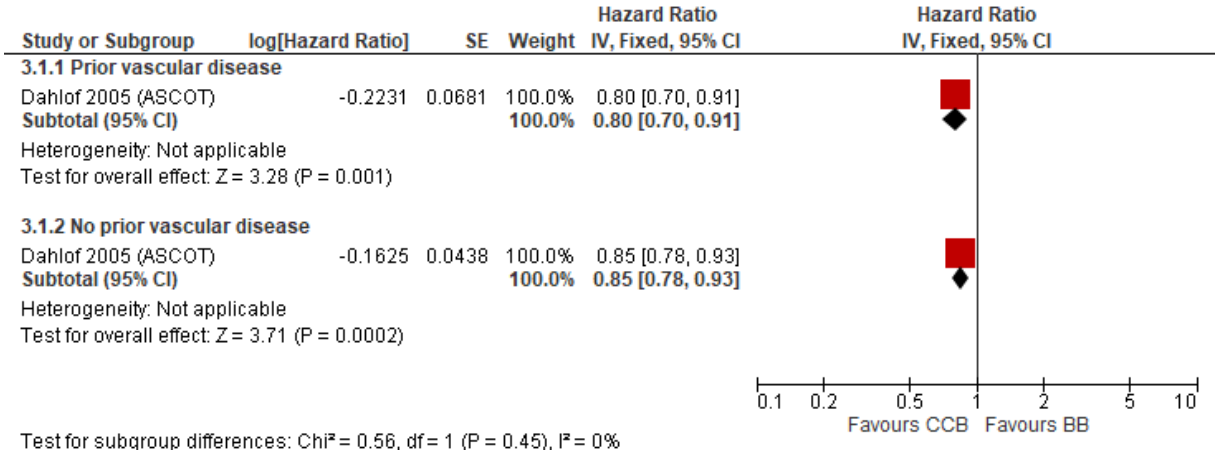
Figure 18: Hospitalisation for angina in those with and without MI history



B.3 CVD history subgroup analyses: calcium channel blocker versus beta blocker

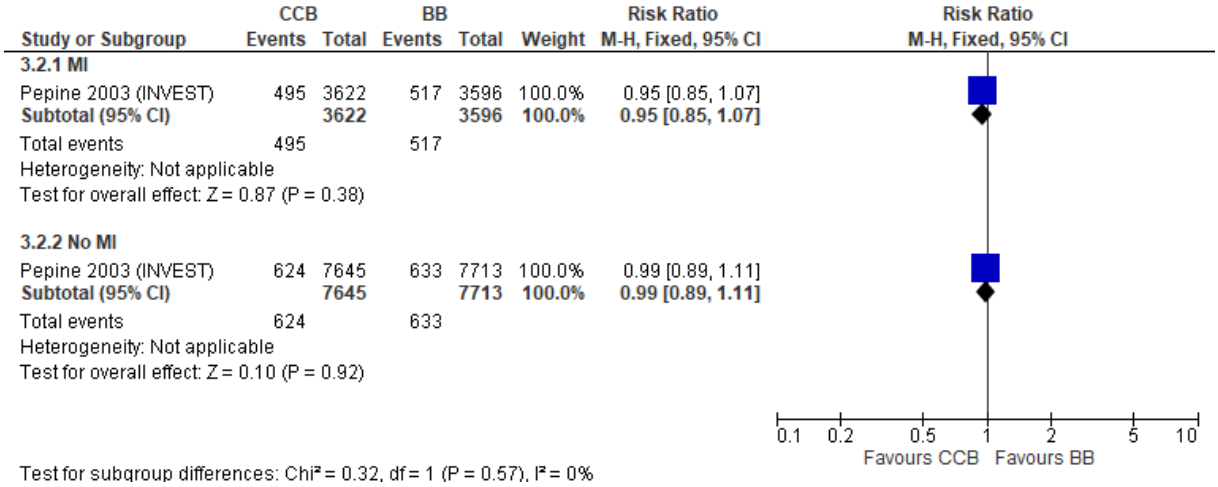
B.3.1 Presence or absence of history of vascular disease

Figure 19: Cardiovascular events and procedures in those with and without prior vascular disease



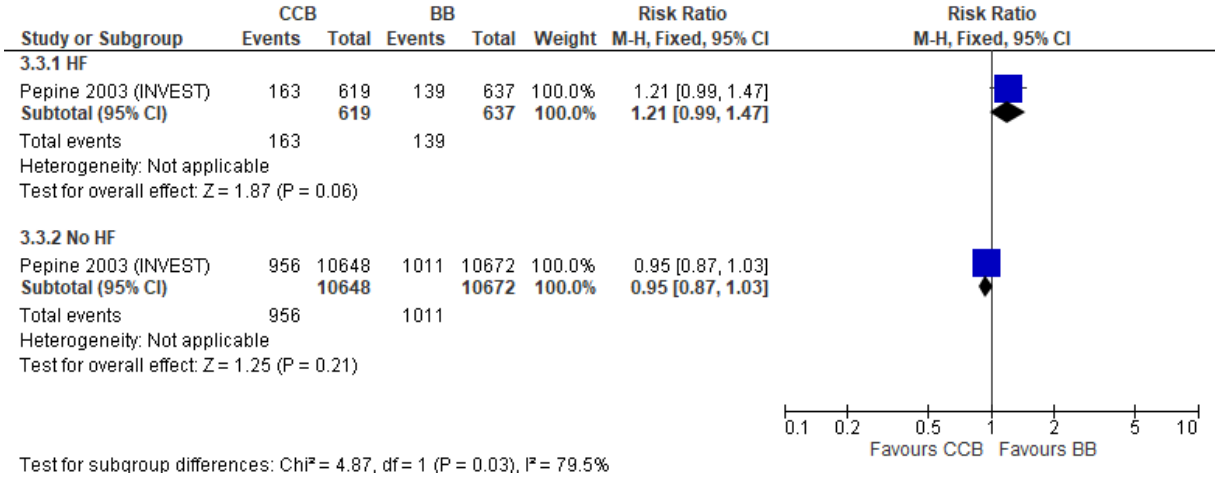
B.3.2 Presence or absence of history of myocardial infarction (MI)

Figure 20: First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) in those with and without history of MI



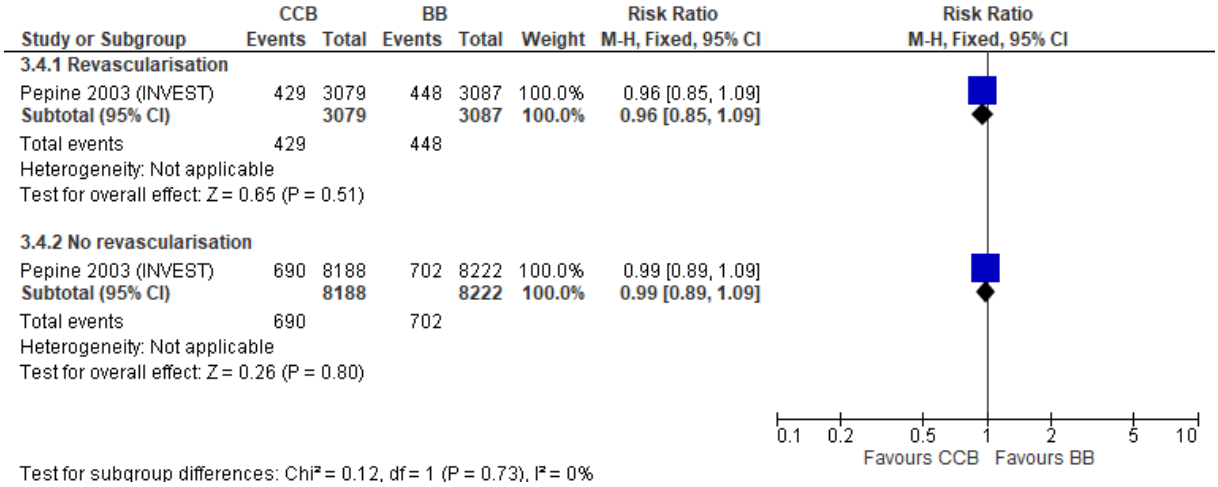
B.3.3 Presence or absence of history of heart failure

Figure 21: First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) in those with and without history of heart failure



B.3.4 Presence or absence of history of revascularisation

Figure 22: First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) in those with and without history of revascularisation



B.4 Treatment efficacy after stroke: thiazide-like diuretics versus placebo [outcome data from previous guideline versions]

Figure 23: All-cause mortality in those with history of stroke/TIA

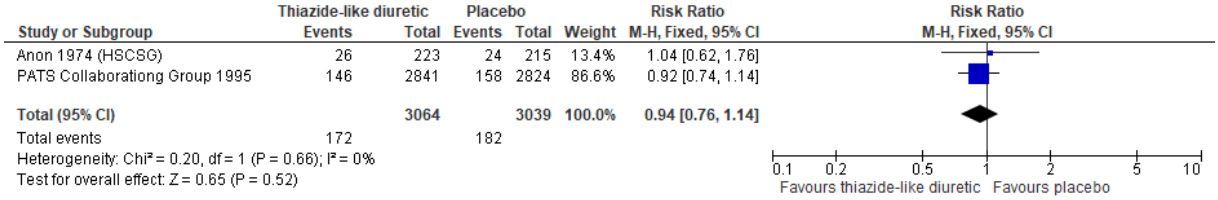


Figure 24: Coronary heart disease events (MI or sudden death) in those with history of stroke/TIA

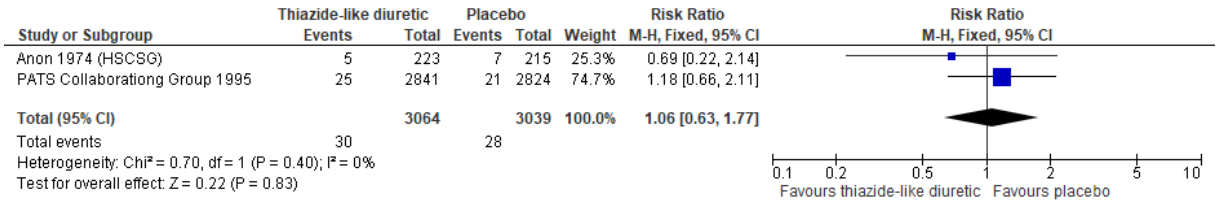


Figure 25: Stroke recurrence in those with history of stroke/TIA

Figure 26: Total cardiovascular events in those with history of stroke/TIA

B.5 Treatment efficacy after stroke: beta blocker versus placebo [outcome data from previous guideline versions]

Figure 27: All-cause mortality in those with history of stroke/TIA

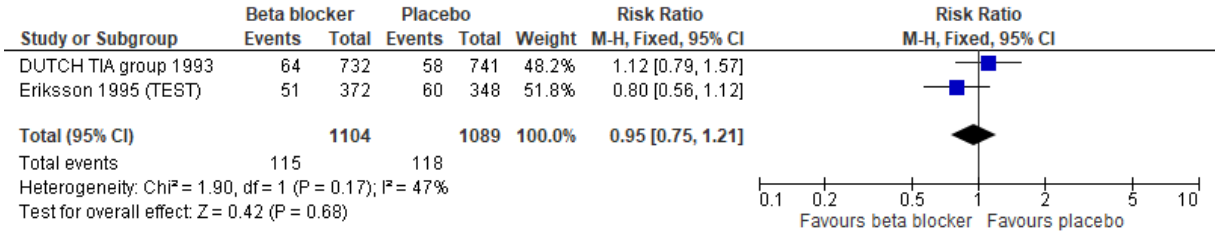


Figure 28: Coronary heart disease events (cardiac death or non-fatal MI) in those with history of stroke/TIA

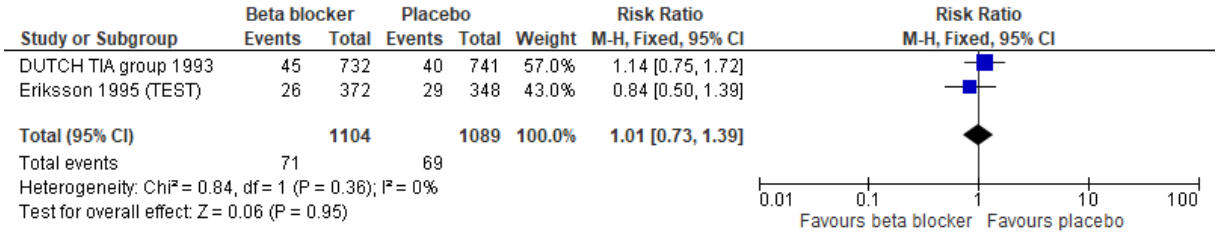
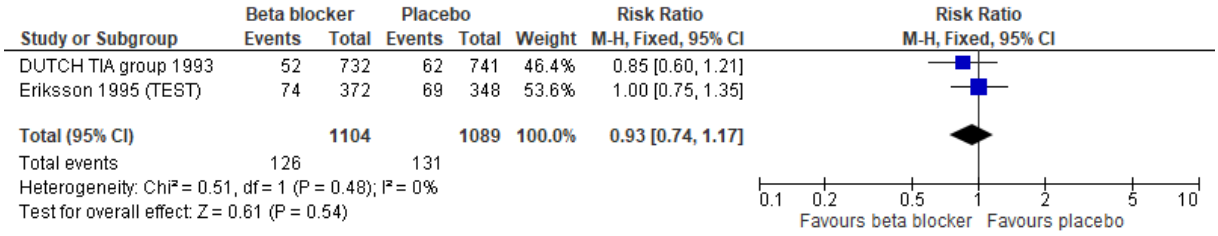


Figure 29: Fatal or non-fatal stroke in those with history of stroke/TIA



B.6 Treatment efficacy after stroke: ACE inhibitors (ACEI) versus placebo [outcome data from previous guideline versions]

Figure 30: All-cause mortality in those with history of stroke/TIA

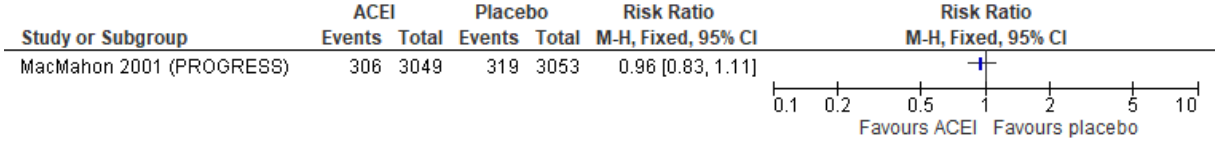


Figure 31: Coronary heart disease events (non-fatal MI or death from coronary heart disease) in those with history of stroke/TIA

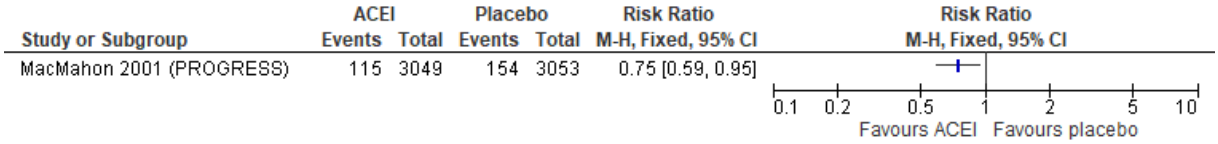


Figure 32: Fatal or non-fatal stroke in those with history of stroke/TIA

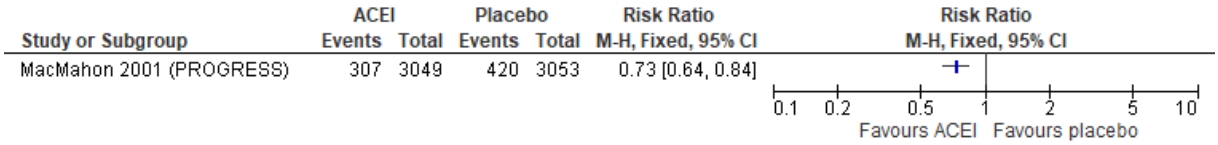
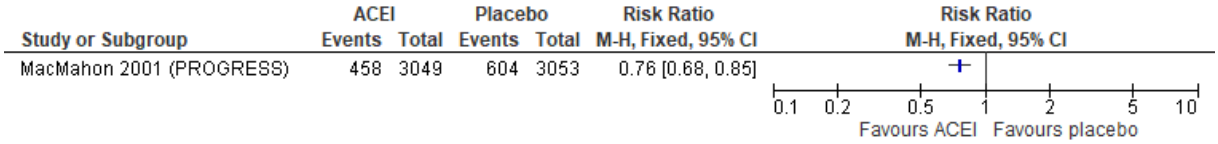


Figure 33: Total major vascular events (vascular death, non-fatal MI, non-fatal stroke) in those with history of stroke/TIA



B.7 Treatment efficacy in those with a history of coronary artery disease: calcium channel blocker (CCB) versus ACE inhibitor (ACEI) [outcome data from previous guideline versions]

Figure 34: All-cause mortality in those with history of coronary artery disease

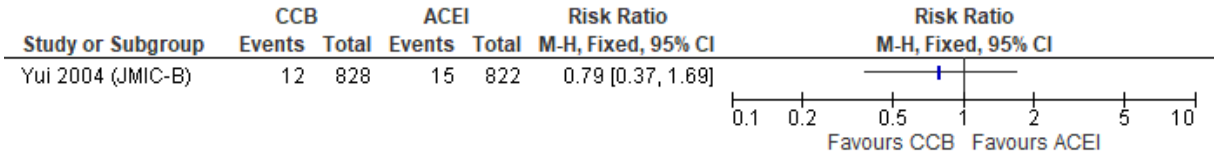


Figure 35: Myocardial infarction in those with history of coronary artery disease

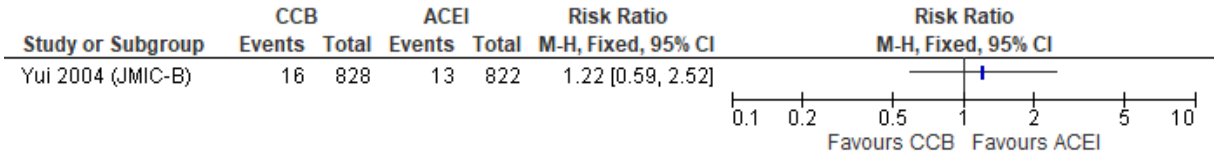


Figure 36: Stroke in those with history of coronary artery disease

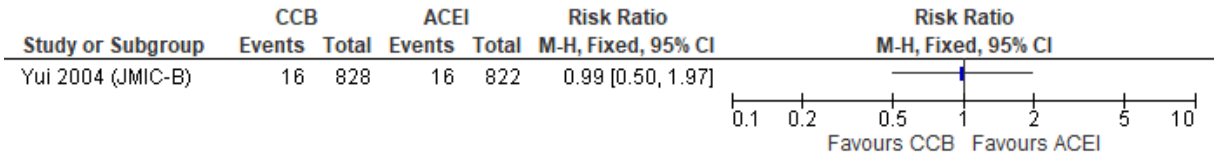


Figure 37: Total cardiac events in those with history of coronary artery disease

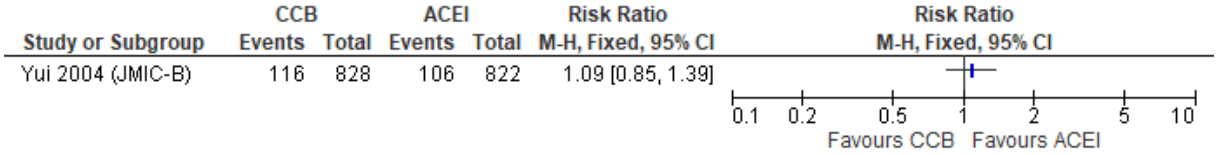


Figure 38: Heart failure requiring hospitalisation in those with history of coronary artery disease

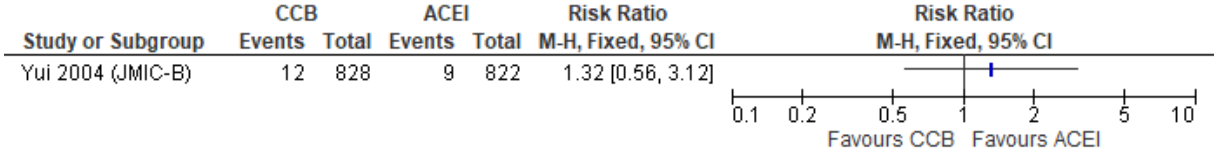
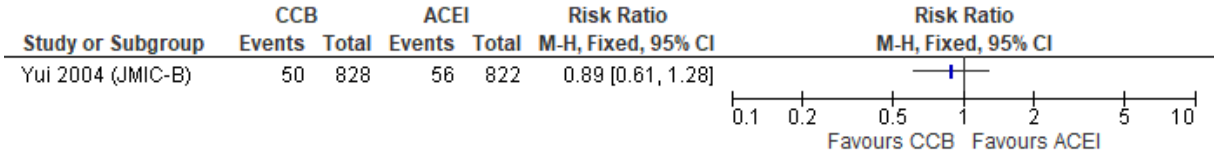


Figure 39: Angina requiring hospitalisation in those with history of coronary artery disease



B.8 Treatment efficacy in those with a history of coronary artery disease: calcium channel blocker (CCB) versus beta blocker (BB) [outcome data from previous guideline versions]

Figure 40: All-cause mortality in those with history of coronary artery disease

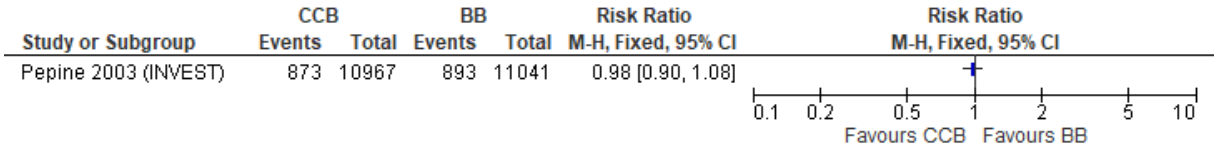


Figure 41: Non-fatal MI in those with history of coronary artery disease

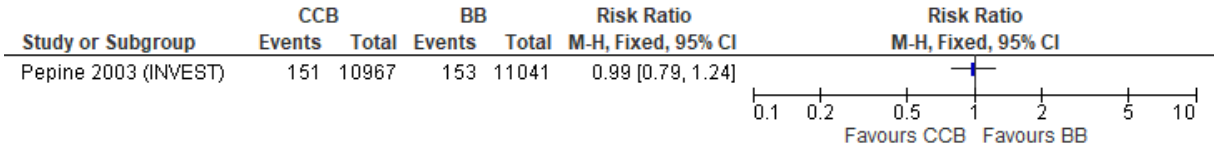
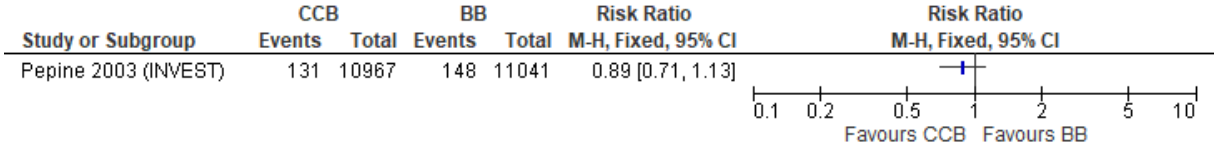


Figure 42: Non-fatal stroke in those with history of coronary artery disease



Appendix C GRADE tables

C.1 Subgroup analyses for those with and without a history of CVD

Table 41: Clinical evidence profile: thiazide-like diuretic versus placebo

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide-like diuretic	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
Coronary heart disease - with MI history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	6/113 (5.3%)	9/116 (7.8%)	RR 0.68 (0.25 to 1.86)	25 fewer per 1,000 (from 58 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Coronary heart disease - No MI history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	94/2196 (4.3%)	125/2207 (5.7%)	RR 0.76 (0.58 to 0.98)	14 fewer per 1,000 (from 24 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	
Heart failure - with MI history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	6/113 (5.3%)	13/116 (11.2%)	RR 0.47 (0.19 to 1.20)	59 fewer per 1,000 (from 91 fewer to 22 more)	⨁◯◯◯ VERY LOW	
Heart failure - No MI history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	50/2196 (2.3%)	90/2207 (4.1%)	RR 0.56 (0.40 to 0.78)	18 fewer per 1,000 (from 24 fewer to 9 fewer)	⨁◯◯◯ VERY LOW	
Stroke - with MI history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	4/113 (3.5%)	6/116 (5.2%)	RR 0.68 (0.20 to 2.36)	17 fewer per 1,000 (from 41 fewer to 70 more)	⨁◯◯◯ VERY LOW	
Stroke - No MI history (follow up: mean 4.5 years)												

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide-like diuretic	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	98/2196 (4.5%)	153/2207 (6.9%)	RR 0.64 (0.50 to 0.82)	25 fewer per 1,000 (from 35 fewer to 12 fewer)	⊕◯◯◯ VERY LOW	
Coronary heart disease - with stroke history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	2/35 (5.7%)	1/30 (3.3%)	RR 1.71 (0.16 to 17.98)	24 more per 1,000 (from 28 fewer to 566 more)	⊕◯◯◯ VERY LOW	
Coronary heart disease - No stroke history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	98/2274 (4.3%)	133/2293 (5.8%)	RR 0.74 (0.58 to 0.96)	15 fewer per 1,000 (from 24 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	
Heart failure - with stroke history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	1/35 (2.9%)	3/30 (10.0%)	RR 0.29 (0.03 to 2.60)	71 fewer per 1,000 (from 97 fewer to 160 more)	⊕◯◯◯ VERY LOW	
Heart failure - No stroke history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	53/2274 (2.3%)	100/2293 (4.4%)	RR 0.53 (0.39 to 0.74)	20 fewer per 1,000 (from 27 fewer to 11 fewer)	⊕⊕◯◯ LOW	
Stroke - with prior stroke (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	4/35 (11.4%)	5/30 (16.7%)	RR 0.69 (0.20 to 2.32)	52 fewer per 1,000 (from 133 fewer to 220 more)	⊕◯◯◯ VERY LOW	
Stroke - No stroke history (follow up: mean 4.5 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	98/2274 (4.3%)	154/2293 (6.7%)	RR 0.64 (0.50 to 0.82)	24 fewer per 1,000 (from 34 fewer to 12 fewer)	⊕◯◯◯ VERY LOW	

a. High attrition bias (withdrawals) and high proportion of those in placebo group received active treatment. Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crossed both MIDs

c. 95% CI crosses one MID

Table 42: Clinical evidence profile: calcium channel blocker versus ACE inhibitor

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	ACE inhibitor	Relative (95% CI)	Absolute (95% CI)	Certainty	
Mortality - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [b]	none	358/2202 (16.3%)	418/2270 (18.4%)	RR 0.88 (0.78 to 1.00)	22 fewer per 1,000 (from 41 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	
Mortality - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious [b]	none	882/6777 (13.0%)	883/6715 (13.1%)	RR 0.99 (0.91 to 1.08)	1 fewer per 1,000 (from 12 fewer to 11 more)	⊕⊕◯◯ LOW	
Coronary heart disease - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	282/2202 (12.8%)	300/2270 (13.2%)	RR 0.97 (0.83 to 1.13)	4 fewer per 1,000 (from 22 fewer to 17 more)	⊕⊕◯◯ LOW	
Coronary heart disease events - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	507/6777 (7.5%)	494/6715 (7.4%)	RR 1.02 (0.90 to 1.15)	1 more per 1,000 (from 7 fewer to 11 more)	⊕⊕◯◯ LOW	
Stroke - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	105/2202 (4.8%)	138/2270 (6.1%)	RR 0.78 (0.61 to 1.00)	13 fewer per 1,000 (from 24 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	
Stroke - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	268/6777 (4.0%)	314/6715 (4.7%)	RR 0.85 (0.72 to 0.99)	7 fewer per 1,000 (from 13 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	
Heart failure - CHD at baseline (follow up: mean 4.9 years)												

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	ACE inhibitor	Relative (95% CI)	Absolute (95% CI)	Certainty	
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	250/2202 (11.4%)	231/2270 (10.2%)	RR 1.12 (0.94 to 1.32)	12 more per 1,000 (from 6 fewer to 33 more)	⊕◯◯◯ VERY LOW	
Heart failure - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	453/6777 (6.7%)	377/6715 (5.6%)	RR 1.19 (1.04 to 1.36)	11 more per 1,000 (from 2 more to 20 more)	⊕◯◯◯ VERY LOW	
Angina - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	467/2202 (21.2%)	469/2270 (20.7%)	RR 1.03 (0.92 to 1.15)	6 more per 1,000 (from 17 fewer to 31 more)	⊕⊕◯◯ LOW	
Angina - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	474/6777 (7.0%)	538/6715 (8.0%)	RR 0.87 (0.78 to 0.98)	10 fewer per 1,000 (from 18 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	
Coronary revascularisation - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	308/2202 (14.0%)	319/2270 (14.1%)	RR 1.00 (0.86 to 1.15)	0 fewer per 1,000 (from 20 fewer to 21 more)	⊕⊕◯◯ LOW	
Coronary revascularisation - No CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	410/6777 (6.0%)	394/6715 (5.9%)	RR 1.03 (0.90 to 1.18)	2 more per 1,000 (from 6 fewer to 11 more)	⊕⊕◯◯ LOW	
Peripheral arterial disease - CHD at baseline (follow up: mean 4.9 years)												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	109/2202 (5.0%)	102/2270 (4.5%)	RR 1.10 (0.85 to 1.43)	4 more per 1,000 (from 7 fewer to 19 more)	⊕◯◯◯ VERY LOW	
Peripheral arterial disease - No CHD at baseline (follow up: mean 4.9 years)												

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CCB**	**ACE inhibitor**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	153/6777 (2.3%)	207/6715 (3.1%)	RR 0.73 (0.60 to 0.90)	8 fewer per 1,000 (from 12 fewer to 3 fewer)	⊕◯◯◯ VERY LOW	
Cardiac events - History of MI (follow up: mean 3 years)												
1	observational studies	serious [d]	not serious	not serious	very serious [e]	none	315	381	HR 0.91 (0.63 to 1.31)	-	⊕◯◯◯ VERY LOW	
Cardiac events - No history of MI (follow up: mean 3 years)												
1	observational studies	serious [d]	not serious	not serious	serious [c]	none	513	441	HR 1.26 (0.85 to 1.87)	-	⊕◯◯◯ VERY LOW	
Hospitalisation for angina - History of MI (follow up: mean 3 years)												
1	observational studies	serious [d]	not serious	not serious	serious [c]	none	315	381	HR 0.42 (0.22 to 0.80)	-	⊕⊕◯◯ LOW	
Hospitalisation for angina - No history of MI (follow up: mean 3 years)												
1	observational studies	serious [d]	not serious	not serious	very serious [e]	none	513	441	HR 1.29 (0.76 to 2.19)	-	⊕◯◯◯ VERY LOW	

a. High attrition bias (withdrawals greater than event rate). Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crosses the line of no effect
c. 95% CI crosses one MID
d. High attrition bias (withdrawals similar to or greater than event rate). Post-hoc subgroup analysis of RCT adjusted for sex, age, history of myocardial infarction and angina pectoris, but unclear how outcomes were selected.
e. 95% CI crosses both MIDs

Table 43: Clinical evidence profile: calcium channel blocker versus beta blocker

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	BB	Relative (95% CI)	Absolute (95% CI)	Certainty	
CV events and procedures - Prior vascular disease (follow up: median 5.5 years)												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	360/1565 (23.0%)	443/1582 (28.0%)	HR 0.80 (0.70 to 0.91)	49 fewer per 1,000 (from 75 fewer to 22 fewer)	⨁⨁◯◯ LOW	
CV events and procedures - No prior vascular disease (follow up: median 5.5 years)												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	1002/8350 (12.0%)	1159/8279 (14.0%)	HR 0.85 (0.78 to 0.93)	20 fewer per 1,000 (from 29 fewer to 9 fewer)	⨁⨁◯◯ LOW	
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - with MI history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	495/3622 (13.7%)	517/3596 (14.4%)	RR 0.95 (0.85 to 1.07)	7 fewer per 1,000 (from 22 fewer to 10 more)	⨁⨁⨁◯ MODERATE	
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - No MI history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	624/7645 (8.2%)	633/7713 (8.2%)	RR 0.99 (0.89 to 1.11)	1 fewer per 1,000 (from 9 fewer to 9 more)	⨁⨁⨁◯ MODERATE	
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - with heart failure history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	163/619 (26.3%)	139/637 (21.8%)	RR 1.21 (0.99 to 1.47)	46 more per 1,000 (from 2	⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	BB	Relative (95% CI)	Absolute (95% CI)	Certainty	
										fewer to 103 more)		
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - No heart failure history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	956/10648 (9.0%)	1011/10672 (9.5%)	RR 0.95 (0.87 to 1.03)	5 fewer per 1,000 (from 12 fewer to 3 more)	⊕⊕⊕◯ MODERATE	
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - with revascularisation history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	429/3079 (13.9%)	448/3087 (14.5%)	RR 0.96 (0.85 to 1.09)	6 fewer per 1,000 (from 22 fewer to 13 more)	⊕⊕⊕◯ MODERATE	
First event (death, nonfatal MI, nonfatal stroke, CV death, CV hospitalisation) - No revascularisation history (follow up: mean 2.7 years)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	690/8188 (8.4%)	702/8222 (8.5%)	RR 0.99 (0.89 to 1.09)	1 fewer per 1,000 (from 9 fewer to 8 more)	⊕⊕⊕◯ MODERATE	

a. Post-hoc subgroup analysis of RCT with no adjustment for confounding and baseline variables not reported by CVD history status.
b. 95% CI crosses one MID

Table 44: Clinical evidence profile: ACE inhibitor versus angiotensin II receptor blocker

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	ARB	Relative (95% CI)	Absolute (95% CI)	Certainty	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure - Prior cardiovascular disease												

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	ARB	Relative (95% CI)	Absolute (95% CI)	Certainty	
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	15,672	-	Not reported	16.8%	⨁⨁◯◯ LOW	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure – No prior cardiovascular disease												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	1486	-	Not reported	13.1%	⨁⨁◯◯ LOW	

a. Pre-specified subgroup analysis of RCT with insufficient reporting.
b. Imprecision could not be assessed

C.2 Comparative treatment effects in adults with a history of stroke or TIA

Table 45: Clinical evidence profile: thiazide-like diuretic versus placebo in adults with a history of stroke or TIA

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide-like diuretic	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
All-cause mortality												
2	randomised trials	serious [a]	not serious	not serious [b]	serious [c]	none	172/3064 (5.6%)	182/3039 (6.0%)	RR 0.94 (0.76 to 1.14)	4 fewer per 1,000 (from 14 fewer to 8 more)	⨁⨁◯◯ LOW	
Coronary heart disease (MI, or sudden death)												
2	randomised trials	serious [a]	not serious	not serious [b]	very serious [d]	none	30/3064 (1.0%)	28/3039 (0.9%)	RR 1.06 (0.63 to 1.77)	1 more per 1,000 (from 3 fewer to 7 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide-like diuretic	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
Stroke recurrence												
2	randomised trials	serious [a]	not serious	not serious [b]	serious [e]	none	196/3064 (6.4%)	259/3039 (8.5%)	RR 0.75 (0.63 to 0.89)	21 fewer per 1,000 (from 32 fewer to 9 fewer)	⨁⨁◯◯ LOW	
Total cardiovascular events												
2	randomised trials	serious [a]	not serious	not serious [b]	serious [e]	none	206/3064 (6.7%)	266/3039 (8.8%)	RR 0.77 (0.65 to 0.92)	20 fewer per 1,000 (from 31 fewer to 7 fewer)	⨁⨁◯◯ LOW	

a. Majority of the evidence at high risk of selection bias (unclear randomisation method and inadequate allocation concealment).
b. Note: Not all participants in PATS trial had diagnosed hypertension (16% <140/90 mmHg)
c. 95% CI crosses the line of no effect
d. 95% CI crosses both MIDs
e. 95% CI crosses one MID

Table 46: Clinical evidence profile: beta blocker versus placebo in adults with a history of stroke or TIA

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
All-cause mortality												
2	randomised trials	serious [a]	not serious	not serious [b]	serious [c]	none	115/1104 (10.4%)	118/1089 (10.8%)	RR 0.95 (0.75 to 1.21)	5 fewer per 1,000 (from 27 fewer to 23 more)	⨁⨁◯◯ LOW	
CHD events (cardiac death/non-fatal MI)												

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
2	randomised trials	serious [d]	not serious	serious [e]	very serious [f]	none	71/1104 (6.4%)	69/1089 (6.3%)	RR 1.01 (0.73 to 1.39)	1 more per 1,000 (from 17 fewer to 25 more)	⊕◯◯◯ VERY LOW	
Fatal or non-fatal stroke												
2	randomised trials	serious [a]	not serious	not serious [b]	serious [g]	none	126/1104 (11.4%)	131/1089 (12.0%)	RR 0.93 (0.74 to 1.17)	8 fewer per 1,000 (from 31 fewer to 20 more)	⊕⊕◯◯ LOW	

a. High risk of selection bias (1 study unclear and 1 study inadequate allocation concealment).
b. Note: only 29% of Dutch TIA trial had hypertension
c. 95% CI crosses the line of no effect
d. Majority of the evidence at high risk of attrition bias because >40% withdrew from the Dutch TIA study
e. Only 29% of Dutch TIA trial had hypertension
f. 95% CI crosses both MIDs
c. 95% CI crosses 1 MID

Table 47: Clinical evidence profile: ACE inhibitor versus placebo in adults with a history of stroke or TIA

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
All-cause mortality												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	306/3049 (10.0%)	319/3053 (10.4%)	RR 0.96 (0.83 to 1.11)	4 fewer per 1,000 (from 18 fewer to 11 more)	⊕◯◯◯ VERY LOW	
CHD events (non-fatal MI or death from coronary heart disease)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	115/3049 (3.8%)	154/3053 (5.0%)	RR 0.75 (0.59 to 0.95)	13 fewer per 1,000	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	
										(from 21 fewer to 3 fewer)		
Fatal and non-fatal stroke												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	307/3049 (10.1%)	420/3053 (13.8%)	RR 0.73 (0.64 to 0.84)	37 fewer per 1,000 (from 50 fewer to 22 fewer)	⨁◯◯◯ VERY LOW	
Total major vascular events (vascular death, non-fatal MI, non-fatal stroke)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d]	none	458/3049 (15.0%)	604/3053 (19.8%)	RR 0.76 (0.68 to 0.85)	47 fewer per 1,000 (from 63 fewer to 30 fewer)	⨁◯◯◯ VERY LOW	

a. High risk of attrition bias (>30% of participants withdrew from the trial)
b. Population indirectness: only 48% had hypertension
c. 95% CI crosses the line of no effect
d. 95% CI crosses one MID

C.3 Comparative treatment effects in adults with a history of coronary artery disease (CAD)

Table 48: Clinical evidence profile: calcium channel blocker versus ACE inhibitor in adults with a history of CAD

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	ACE inhibitor	Relative (95% CI)	Absolute (95% CI)	Certainty	
All-cause mortality												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	12/828 (1.4%)	15/822 (1.8%)	RR 0.79 (0.37 to 1.69)	4 fewer per 1,000 (from 11 fewer to 13 more)	⨁⨁◯◯ LOW	
MI												

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	ACE inhibitor	Relative (95% CI)	Absolute (95% CI)	Certainty	
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	16/828 (1.9%)	13/822 (1.6%)	RR 1.22 (0.59 to 2.52)	3 more per 1,000 (from 6 fewer to 24 more)	⊕◯◯◯ VERY LOW	
Stroke												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	16/828 (1.9%)	16/822 (1.9%)	RR 0.99 (0.50 to 1.97)	0 fewer per 1,000 (from 10 fewer to 19 more)	⊕◯◯◯ VERY LOW	
Total cardiac events (cardiac death or sudden death; MI; angina requiring hospitalisation; heart failure requiring hospitalization; serious arrhythmia or coronary interventions)												
1	randomised trials	serious [d]	not serious	not serious	serious [e]	none	116/828 (14.0%)	106/822 (12.9%)	RR 1.09 (0.85 to 1.39)	12 more per 1,000 (from 19 fewer to 50 more)	⊕⊕◯◯ LOW	
Heart failure requiring hospitalisation												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	12/828 (1.4%)	9/822 (1.1%)	RR 1.32 (0.56 to 3.12)	4 more per 1,000 (from 5 fewer to 23 more)	⊕◯◯◯ VERY LOW	
Angina requiring hospitalisation												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	50/828 (6.0%)	56/822 (6.8%)	RR 0.89 (0.61 to 1.28)	7 fewer per 1,000 (from 27 fewer to 19 more)	⊕◯◯◯ VERY LOW	

a. Risk of attrition bias because rate of missing data is greater than the number of events.
b. 95% CI crosses the line of no effect
c. 95% CI crosses both MIDs
d. Risk of attrition bias because the level of missing data is comparable with the number of events.
e. 95% CI crosses one MID

Table 49: Clinical evidence profile: calcium channel blocker versus beta blocker in adults with a history of CAD

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	BB	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	873/10967 (8.0%)	893/11041 (8.1%)	RR 0.98 (0.90 to 1.08)	2 fewer per 1,000 (from 8 fewer to 6 more)	⨁⨁⨁◯ MODERATE	
Non-fatal MI												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	151/10967 (1.4%)	153/11041 (1.4%)	RR 0.99 (0.79 to 1.24)	0 fewer per 1,000 (from 3 fewer to 3 more)	⨁⨁⨁◯ MODERATE	
Non-fatal stroke												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	131/10967 (1.2%)	148/11041 (1.3%)	RR 0.89 (0.71 to 1.13)	1 fewer per 1,000 (from 4 fewer to 2 more)	⨁⨁⨁◯ MODERATE	

a. 95% CI crosses the line of no effect
b. 95% CI crosses one MID

Appendix D – Health economic model

Original economic modelling was not undertaken in this area.

Appendix E – Excluded studies

Clinical studies

Studies cited in previous versions of the guideline (with the exception of NG136) but excluded from this report are listed below.

Table 50: Studies excluded from the clinical review

Reference	Reason for exclusion
Anonymous 1991[103]	Not included in guideline meta-analysis because results not reported by treatment group
Elmer 1995[35]	Not included in guideline meta-analysis because results not reported by treatment group
Liebson 1995[58]	Not included in guideline meta-analysis because results not reported by treatment group
Psaty 1997[86]	Systematic review: no sub-analysis for CVD subgroup

Health Economic studies

Studies included in previous versions of the guideline but excluded from this report are listed below.

Table 51: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix F Pharmacological recommendations in NICE guidelines on cardiovascular conditions

Table 52: Summary of existing pharmacological treatment recommendations in NICE guidelines on cardiovascular conditions

Guideline	Population	Recommendations
NG185	Post-myocardial infarction (MI)	1.4.1For secondary prevention, offer people who have had MI treatment with the following drugs: • angiotensin-converting enzyme (ACE) inhibitor • dual antiplatelet therapy (aspirin plus a second antiplatelet) unless they have a separate indication for anticoagulation (see the section on antiplatelet therapy for people with an ongoing separate indication for anticoagulation) • beta-blocker 1.4.4Offer people who present acutely with an MI, an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely. [2013] 1.4.7After an MI, offer people who are intolerant to ACE inhibitors, an angiotensin receptor blocker (ARB) instead of an ACE inhibitor. [2013] 1.4.9Offer an ACE inhibitor to people who have had an MI more than 12 months ago. Titrate to the maximum tolerated or target dose (over a 4- to 6-week period) and continue indefinitely. [2013] 1.4.10Offer people who have had an MI more than 12 months ago and who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor. [2013] 1.4.24Offer people a beta-blocker as soon as possible after an MI, when the person is haemodynamically stable. [2013] 1.4.27Discuss the potential benefits and risks of stopping or continuing beta-blockers beyond 12 months after an MI for people without reduced left ventricular ejection fraction. 1.4.28Continue a beta-blocker indefinitely in people with reduced left ventricular ejection fraction. [2013] 1.4.30Do not offer people without reduced left ventricular ejection fraction or heart failure, who have had an MI more than 12 months ago, treatment with a beta-blocker unless there is an additional clinical indication for a beta blocker. [2013] 1.4.31Do not routinely offer calcium channel blockers to reduce cardiovascular risk after an MI. [2007] 1.4.32If beta-blockers are contraindicated or need to be discontinued, diltiazem or verapamil may be considered for secondary prevention in people without pulmonary congestion or reduced left ventricular ejection fraction. [2007]

Guideline	Population	Recommendations
		1.4.33For people whose condition is stable after an MI, calcium channel blockers may be used to treat hypertension
NG106	Chronic heart failure	First line treatment 1.4.1 Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction. Use clinical judgement when deciding which drug to start first. [2010] 1.4.2 Do not offer ACE inhibitor therapy if there is a clinical suspicion of haemodynamically significant valve disease until the valve disease has been assessed by a specialist. [2003] 1.4.3 Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the target or maximum tolerated dose is reached. [2010] 1.4.4 Measure serum sodium and potassium, and assess renal function, before and 1 to 2 weeks after starting an ACE inhibitor, and after each dose increment. [2010, amended 2018] 1.4.5 Measure blood pressure before and after each dose increment of an ACE inhibitor. 1.4.6 Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010, amended 2018] Alternate treatment 1.4.7 Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. [2010] 1.4.8 Measure serum sodium and potassium, and assess renal function, before and after starting an ARB and after each dose increment. [2010, amended 2018] 1.4.9 Measure blood pressure after each dose increment of an ARB. 1.4.10 Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010, amended 2018] 1.4.11 If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. [2010] Beta-blockers 1.4.12 Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. [2010] 1.4.13 Introduce beta-blockers in a 'start low, go slow' manner. Assess heart rate and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. [2010,amended 2018]

Guideline	Population	Recommendations
		1.4.14 Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. [2010] 1.4.15 Offer a mineralocorticoid receptor antagonist (MRA), in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. [2018] 1.4.20 Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. [2012] 1.4.22 Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. [2016] 1.5.1 For people who have heart failure with reduced ejection fraction and chronic kidney disease with an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 m2 or above: if the person's eGFR is 45 ml/min/1.73 m2 or below, consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin. [2018] Diuretics 1.6.1 Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. [2003] 1.6.2 People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice. [2003, amended 2018] Calcium-channel blockers 1.6.3 Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. [2003, amended 2018]
CG187	Acute HF	1.3 Initial pharmacological treatment 1.3.3 Offer intravenous diuretic therapy to people with acute heart failure. Start treatment using either a bolus or infusion strategy. 1.3.4 For people already taking a diuretic, consider a higher dose of diuretic than that on which the person was admitted unless there are serious concerns with patient adherence to diuretic therapy before admission. 1.3.5 Closely monitor the person's renal function, weight and urine output during diuretic therapy. 1.5 Treatment after stabilisation

Guideline	Population	Recommendations
		1.5.1 In a person presenting with acute heart failure who is already taking beta-blockers, continue the beta-blocker treatment unless they have a heart rate less than 50 beats per minute, second or third degree atrioventricular block, or shock. 1.5.2 Start or restart beta-blocker treatment during hospital admission in people with acute heart failure due to left ventricular systolic dysfunction, once their condition has been stabilised – for example, when intravenous diuretics are no longer needed. 1.5.3 Ensure that the person's condition is stable for typically 48 hours after starting or restarting beta-blockers and before discharging from hospital. 1.5.4 Offer an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker if there are intolerable side effects) and an aldosterone antagonist during hospital admission to people with acute heart failure and reduced left ventricular ejection fraction. If the angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) is not tolerated an aldosterone antagonist should still be offered. 1.5.5 Closely monitor the person's renal function, electrolytes, heart rate, blood pressure and overall clinical status during treatment with beta-blockers, aldosterone antagonists or angiotensin-converting enzyme inhibitors.
CG126	Stable Angina	Drugs for secondary prevention of cardiovascular disease 1.3.6 Consider angiotensin-converting enzyme (ACE) inhibitors for people with stable angina and diabetes. Offer or continue ACE inhibitors for other conditions, in line with relevant NICE guidance. 1.3.8 Offer treatment for high blood pressure in line with Hypertension (NICE clinical guideline 34) [replaced by Hypertension (NICE clinical guideline 127)]. Drugs for treating stable angina 1.4.7 Offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina. Decide which drug to use based on comorbidities, contraindications and the person's preference. 1.4.8 If the person cannot tolerate the beta blocker or calcium channel blocker, consider switching to the other option (calcium channel blocker or beta blocker). 1.4.9 If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker, consider either switching to the other option or using a combination of the two[1]. 1.4.10 Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.
CG147	Peripheral arterial disease	No recommendations on hypertension drugs 1.2.1 Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance on: smoking cessation diet, weight management and exercise lipid modification and statin therapy the prevention, diagnosis and management of diabetes the prevention, diagnosis and management of high blood pressure antiplatelet therapy. [2012]
NG128	Stroke	No recommendations on hypertension drugs Blood pressure control for people with acute intracerebral haemorrhage

Guideline	Population	Recommendations
		1.5.4 Offer rapid blood pressure lowering to people with acute intracerebral haemorrhage who do not have any of the exclusions listed in recommendation 1.5.6 and who: present within 6 hours of symptom onset and have a systolic blood pressure between 150 and 220 mmHg. Aim for a systolic blood pressure target of 130 to 140 mmHg within 1 hour of starting treatment and maintain this blood pressure for at least 7 days. [2019] 1.5.5 Consider rapid blood pressure lowering for people with acute intracerebral haemorrhage who do not have any of the exclusions listed in recommendation 1.5.6 and who: present beyond 6 hours of symptom onset or have a systolic blood pressure greater than 220 mmHg. [2019] Aim for a systolic blood pressure target of 130 to 140 mmHg within 1 hour of starting treatment and maintain this blood pressure for at least 7 days. [2019] 1.5.6 Do not offer rapid blood pressure lowering to people who: have an underlying structural cause (for example, tumour, arteriovenous malformation or aneurysm) have a score on the Glasgow Coma Scale of below 6 are going to have early neurosurgery to evacuate the haematoma have a massive haematoma with a poor expected prognosis. [2019] Blood pressure control for people with acute ischaemic stroke 1.5.7 Anti-hypertensive treatment in people with acute ischaemic stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues: hypertensive encephalopathy hypertensive nephropathy hypertensive cardiac failure/myocardial infarction aortic dissection pre-eclampsia/eclampsia. [2008, amended 2019] 1.5.8 Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for intravenous thrombolysis. [2008]
NG156	Abdominal aortic aneurysm	No pharmacological recommendations.