The National Collaborating Centre

for Chronic Conditions

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HYPERTENSION

Management in adults in primary care: pharmacological update

This is a pharmacological update of *NICE Clinical Guideline 18* (published August 2004, see **www.nice.org.uk/CG018**). The recommendations in this update replace the recommendations on pharmacological interventions for hypertension (section 1.4 of the original NICE guideline, pp103–139). No other recommendations are affected.

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1 Pharmacological interventions

1.1 Introduction

This rapid update of the NICE guideline on hypertension in primary care was undertaken because recent large clinical outcome trials had provided new information about the pharmacological treatment of hypertension. The remit was therefore very specific, focusing only on the recommendations on the pharmacological management of hypertension contained in Chapter 1.4 of the original NICE guideline. Guidance on other issues, for example the target value for starting treatment contained in recommendation 1.4.1, was not considered by this review and remains current.

The work was undertaken by the National Collaborating Centre for Chronic Conditions, based at the Royal College of Physicians of London, with two aims: to incorporate new evidence into the National Institute for Health and Clinical Excellence (NICE) guideline, and to collaborate with the British Hypertension Society (BHS) to produce new joint advice for primary care prescribers in the NHS.

~~1.2 Clinical evidence~~

~~1.2.1 Methodological introduction~~

- ~~Study inclusion and reporting criteria~~

~~A systematic search of the literature was performed on EMBASE and MEDLINE for randomised controlled trials 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).~~

~~Placebo-controlled studies were not included because the main aim of this rapid partial update was to make recommendations regarding the optimal sequencing of drug treatment for hypertension, for which head-to-head studies are required, and because sufficient placebo-controlled studies of the main drug classes had been considered in the original NICE guideline. However, placebo-controlled studies were sought for isolated systolic hypertension because of a lack of comparator studies.~~

~~The cut-off date for evidence to be considered in the previous guideline was July 2004, so this update only searched for English-language titles published after that date. Papers published up to and including 19 December 2005 were considered – this constitutes the cut-off for evidence for this rapid update.~~

Studies were excluded due to:

- inadequate or no randomisation
- inadequate study power, defined as a sample size of less than 200 patients, or having a follow-up period of less than 12 months
- having an exclusive diabetic or paediatric patient population, unrepresentative of the general UK hypertensive population
- stroke, myocardial infarction, and mortality outcomes not being reported.

The following outcomes were recorded for each study, where available:

- 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)
- study drug withdrawal.

Interpretation and analysis of results

All outcomes, with the exception of study drug withdrawal, vascular procedures and unstable angina, were entered into a meta-analysis for each drug combination using RevMan 4.2 software (©The Nordic Cochrane Centre). The overall effect size was reported as the relative risk (RR) with 95% confidence intervals in each case.

A p-value less than 0.05 was considered as statistically significant for overall effect. Forest plots for each comparison are included in Appendix A.

In recording the outcomes, stroke was considered to be synonymous with 'cerebrovascular event'. Reports of 'cardiovascular events' or other composite outcomes other than those listed above were not considered.

Sensitivity analyses were performed based on the inclusion and exclusion of silent myocardial infarction and the inclusion and exclusion of secondary prevention studies. Additional subgroup analyses were performed to identify the source of any significant heterogeneity in study results (defined as an I^2 statistic greater than 50%).

Where the heterogeneity has I^2 greater than 50%, the trials are reported individually in the evidence statements.

The following outcomes were not subject to meta-analysis due to potential variability or subjectivity in diagnosis or treatment protocols, and were reported as a narrative only:

- unstable angina
- revascularisation procedures
- study drug withdrawal.

Following consultation on the draft guideline, heart failure as an outcome was included in the meta-analysis. Because of inconsistency in definition of heart failure in the trials, this was analysed using a random effects model.

▷ Secondary analyses

In addition to results in general hypertensive populations, the following subgroups were also considered separately:

- those patients with isolated systolic hypertension (ISH)
- black patients
- younger patients (defined as under 55 years).

For ISH, due to the lack of evidence comparing different antihypertensive drugs, the results from placebo-controlled trials were also considered. These results included pre-defined subgroup analyses from trials in general hypertensive populations as well as one trial comprising only ISH patients. The results were entered into a meta-analysis according to the same procedure specified above. The definition of ISH varied slightly between studies: permitting a diastolic blood pressure up to 95 mmHg in one study (SYST-EUR[1–3]) and 90 mmHg in the others (SHEP,[4–7] SHEP-P[8–10]).

No trials comprising only non-white patients were found, although two pre-defined subgroup analyses from trials in general hypertensive populations were found (ALLHAT,[11–13] LIFE[14–21]). Results involving placebo comparisons in non-white populations were not considered.

Evidence on younger patients was extremely sparse, and evidence consideration was therefore extended to include papers pre-dating July 2004 and in which blood pressure lowering effect was the main outcome measure.

▷ Study characteristics

A total of 20 studies were found that satisfied the inclusion criteria for comparisons involving the above five drug classes, and of these, four (ASCOT,[22] JMIC-B,[23,24] PHYLLIS,[25] and VALUE[26]) were new studies not included in the original guideline (see Table 1).

Table 1 Characteristics of included studies

Trial	Year published	I1 Drug	I2 Drug	Secondary drugs	I1 n	I2 n
ALLHAT[11–13]	2002	ACEi: lisinopril	CCB: amlodipine	BB/CAA	8778	8790
ALLHAT[11–13]	2002	ACEi: lisinopril	TD: chlorthalidone	BB/CAA	8778	14836
ALLHAT[11–13]	2002	CCB: amlodipine	TD: chlorthalidone	BB/CAA	8790	14836
ANBP2[27]	2003	ACEi: enalapril	TD: hydrochlorothiazide	BB/CCB/ARB	3044	3037
ASCOT[22]	2005	BB: atenolol	CCB: amlodipine	TD/ACEi	9618	9639
ELSA[28]	2002	BB: atenolol	CCB: lacidipine	TD	114	1128
HAPPHY[29]	1987	BB: atenolol/ metoprolol	TD: bendrofluazide/ hydrochlorothiazide	LD+VD	3265	3240
INSIGHT[30,31]	2000	CCB: nifedipine	TD: co-amilozide (hydrochlorothiazide)	BB/ACEi	3223	3203

continued

Table 1 Characteristics of included studies – *continued*

Trial	Year published	I1 Drug	I2 Drug	Secondary drugs	I1 n	I2 n
INVEST[32]	2003	BB+ACEi: atenolol + trandolapril*	CCB+ACEi: verapamil + trandolapril*	TD/ACEi	11041	10967
JMIC-B[23,24]	2004	ACEi: enalapril/ imidapril	CCB: nifedipine retard	AB	822	828
LIFE[14–18]	2002	ARB: losartan	BB: atenolol	TD	4557	4546
MIDAS[33]	1998	CCB: isradipine	TD: hydrochlorothiazide	ACEi	442	441
MRC[34]	1985	BB: propranolol	TD: bendroflumethiazide	CAA	3558	3519
MRC-O[35]	1992	BB: atenolol	TD: hydrochlorothiazide (+amiloride)	BB/TD/CCB**	1102	1081
NICS-EH[36]	1999	CCB: nicardipine hydrochloride	TD: triclormethiazide	Not reported	204	210
PHYLLIS[25]	2004	ACEi: fosinopril (+pravastatin)	TD: hydrochlorothiazide (+pravastatin)	CCB	254	253
SHEP-P[8–10]	1985	TD: chlorthalidone	Placebo	Reserpine,BB, hydralazine	443	108
SHEP[4–7]	1991	TD: chlorthalidone	Placebo	BB, reserpine	2365	2371
STOP-H2[37–40]	1999	ACEi: enalapril/ lisinopril	CCB: felodipine/isradipine	TD/BB	2205	2196
SYST-EUR[1–3]	2000	CCB: nitrendipine	Placebo	ACEi, TD	2398	2297
VALUE[26]	2004	CCB: amlodipine	ARB: valsartan	TD	7596	7649
VHAS[41,42]	1998	CCB: verapamil	TD: chlorthalidone	ACE	707	707

Trial = trial acronym; I1 Drug/I2 Drug = first-line antihypertensive drugs involved in the first/second intervention arm of the study (ordered alphabetically by drug class left to right); Secondary drugs = second- and/or third-line antihypertensive drug classes permitted by the study protocol; I1/I2 n = total number of patients in the first/second intervention arm of the study;
AB = alpha blocking drug; ACEi = ACE inhibitor; ARB = angiotensin II receptor antagonist (also known as angiotensin receptor blockers); BB = beta-blocker; CAA = centrally acting antihypertensive drug; CCB = calcium-channel blocker; LD = loop diuretic; TD = thiazide-type diuretic; VD = vasodilating antihypertensive drug.
*Second drug administered alongside first drug in patients with diabetes, heart failure or renal failure.
**Although second-line agents included study drugs, the effect of this confounding factor was considered to be relatively small given the small percentages of combined use of each study drug (11% in the TD arm and 16% in the BB arm).

Most studies reported comparisons involving two or more drug classes in each treatment arm administered according to a stepped administration protocol. In such cases, an initial antihypertensive drug would be administered, followed by either:

- an increase in the dosage of the first drug, and/or
- the addition of a second drug if blood pressure targets were not reached using the first drug alone.

All results should therefore be interpreted as demonstrating the efficacy and tolerability of each drug only when used as the initial step in a wider antihypertensive drug treatment regimen.

Many studies permitted a third drug to be added in patients unresponsive to both primary and secondary antihypertensive drugs. Such drugs typically included alpha-blocking drugs such as doxazosin or centrally acting antihypertensive drugs such as clonidine.

The update search found no new studies comparing ACE inhibitors or angiotensin-II receptor antagonists with beta-blockers, or comparing ACE inhibitors with ARBs.

Three studies (CONVINCE,[43,44] NORDIL[45,46] and CAPPP[47–49]) included in the original guideline were excluded due to the confounded use of either beta-blocker or thiazide diuretic as first line antihypertensive therapy within the same treatment arm. A fourth study (MAPHY)[50] was a post-hoc follow-up of a subgroup of patients already included in the HAPPHY study,[29] and so was excluded from the update.

One new study (MOSES)[51] identified by the update search was excluded as it reported the primary end-point as a composite of all-cause mortality, cardiovascular, and cerebrovascular events, including all recurrent events, rather than as the first event only.

1.2.2 Clinical evidence statements: head-to-head drug comparisons

Beta-blockers versus thiazide-type diuretics	Level
Three studies (HAPPHY,[29] MRC,[34] MRC-0[35]) were found comparing the efficacy of beta-blockers and thiazide-type diuretics. One study (HAPPHY) included only male patients. A meta-analysis of these three studies showed no significant difference between the two drug classes in terms of mortality.	I
Heterogeneity in the study results (I^2 >75%) suggested that a meta-analysis would be inappropriate for the outcomes of myocardial infarction and stroke. Sensitivity analyses were performed for variation between the studies in terms of age (by including/excluding MRC-0,[35] in which the average age of participants was 70) and gender (by including/excluding HAPPHY),[29] but these were unable to account for the observed heterogeneity. One study (MRC-0)[35] found beta-blockers to be associated with a higher incidence of myocardial infarction compared to thiazide-type diuretics (RR 1.63, 95% CI 1.15 to 2.32). No association was found in the other two studies,[29,34] which considered younger patients. One study (MRC)[34] in a relatively young population (average age 52 years) found beta-blockers to be associated with a higher incidence of stroke compared to thiazide-type diuretics (RR 2.31, 95% CI 1.33 to 4.00). However, no association was found in the other two studies.[29,35] In terms of the frequency of withdrawal of the study drug, two studies (MRC,[34] MRC-0[35]) found beta-blockers to be associated with more withdrawals (RR 1.06, 95% CI 1.01 to 1.11; RR 1.29, 95% CI 1.22 to 1.37) while the remaining study[29] reported a non-significant result.	II
ACE inhibitors versus calcium-channel blockers	
A meta-analysis of three studies (ALLHAT,[11–13] JMIC-B,[23,24] STOP-H2[37–40]) comparing ACE inhibitors with calcium-channel blockers (CCBs) showed that ACE inhibitors were associated with a higher incidence of stroke (RR 1.14, 95% CI 1.02 to 1.28) but a lower incidence of new-onset diabetes (RR 0.85, 95% CI 0.75 to 0.98) and heart failure (RR 0.85, 95% CI 0.78 to 0.93). No significant difference was found for mortality.	I

continued

ACE inhibitors versus calcium-channel blockers – *continued*	**Level**
For MI there was substantial heterogeneity among the studies (I^2 = 69%). Two studies (ALLHAT,[11–13] JMIC-B[23,24]) found no significant difference between study drugs in terms of MI incidence, while a third study (STOP-H2[37–40]) found that ACE inhibitors were associated with a reduced incidence of MI (RR 0.77, 95% CI 0.62 to 0.96). Of the two studies (ALLHAT,[11–13] JMIC-B[23,24]) reporting the outcomes of unstable angina and revascularisation procedures, neither found any significant difference. The two studies (ALLHAT,[11–13] STOP-H2[37–40]) that reported the frequency of study drug withdrawals each found ACE inhibitors to be associated with more withdrawals than CCBs (respectively: RR 1.17, 95% CI 1.12 to 1.23; RR 1.14, 95% CI 1.06 to 1.24).	**II**
Angiotensin-II receptor antagonists versus beta-blockers	
One study (LIFE)[14–21] was found comparing the angiotensin-II receptor antagonist (ARB) losartan with the beta-blocker atenolol as first-line antihypertensive therapy. The study found no significant difference between the two treatments in terms of myocardial infarction, revascularisation procedures, heart failure or angina. However, the study did find ARBs to be associated with a reduced incidence of stroke (RR 0.75, 95% CI 0.63 to 0.88), new-onset diabetes (RR 0.75, 95% CI 0.64 to 0.88) and fewer study drug withdrawals (RR 0.86, 95% CI 0.82 to 0.91). Although mortality was lower in the ARB treatment group, this result was not statistically significant.	**I**
ARBs versus calcium-channel blockers	
One study (VALUE)[26] was found comparing ARBs with CCBs when used as first-line antihypertensive therapy. ARBs were associated with a higher incidence of MI compared to CCBs (RR 1.17, 95% CI 1.01 to 1.36). There was no significant difference in stroke reduction, mortality or incidence of heart failure. The study also reported frequencies of adverse events for each drug class and showed several differences, but overall these did not particularly favour either drug. Pre-specified adverse events for ARBs versus CCBs included peripheral oedema (14.9% versus 32.9%, p<0.0001), dizziness (16.5% versus 14.3%, p<0.0001) and headache (14.7% versus 12.5%, p<0.0001). Additional adverse events identified included diarrhoea (8.8% versus 6.8%, p<0.0001), serious cases of angina (4.4% versus 3.1%, p<0.0001) and syncope (1.7% versus 1.0 %, p<0.0001).	**II**
ACE inhibitors versus thiazide-type diuretics	
A meta-analysis of three studies (ANBP2,[27] ALLHAT,[11–13] PHYLLIS[25]) comparing ACE inhibitors with thiazide-type diuretics showed that ACE inhibitors are associated with a higher incidence of stroke than thiazide-type diuretics (RR 1.13, 95% CI 1.02 to 1.25). However, no difference was found for mortality.	**I**
For MI, the studies are heterogeneous (I^2 = 66.5%). One study based in a relatively elderly and predominantly white population (ANBP2)[27] reported a lower incidence of MI for ACE inhibitors (RR 0.71, 95% CI 0.51 to 0.98), but the remaining studies (ALLHAT,[11–13] PHYLLIS[25]) found no significant difference. For heart failure, a meta-analysis of two studies (ALLHAT,[11–13] ANBP2[27]) also demonstrated heterogeneity (I^2 = 67.1%). ALLHAT[11–13] reported a higher incidence with ACE inhibitors than thiazide-type diuretics (RR 1.19, 95% CI 1.08 to 1.31), but in ANBP2[27] there was no significant difference. One study (ALLHAT)[11–13] reported no significant difference in unstable angina but a higher incidence of revascularisation procedures (RR 1.10, 95% CI 1.00 to 1.21) with ACE inhibitors. Both studies (ALLHAT[11–13] and ANBP2[27]) found ACE inhibitors to be associated with a higher incidence of withdrawal compared to thiazide-type diuretics (RR 1.12, 95% CI 1.08 to 1.17; RR 1.10, 95% CI 1.04 to 1.17).	**II**

continued

ACE inhibitors versus thiazide-type diuretics – *continued*	Level
One study (ALLHAT)[11–13] reported new-onset diabetes as an outcome, and found that the incidence of diabetes after four years of follow-up was significantly higher for thiazide-type diuretics compared to ACE inhibitors ($p<0.001$).	
Calcium-channel blockers versus beta-blockers	
A meta-analysis of three studies (ASCOT,[22] ELSA,[28] INVEST[32]) compared calcium-channel blockers (CCBs) with beta-blockers. There was no statistically significant difference in mortality or myocardial infarction. Based on the results of the two studies reporting stroke as an outcome (ASCOT,[22] ELSA[28]), CCBs were associated with a reduced incidence of stroke (RR 0.77, 95% CI 0.67 to 0.88).	I
For heart failure, a meta-analysis of two studies (ASCOT,[22] INVEST[32]) showed substantial heterogeneity ($I^2 = 67.4\%$), but neither study alone found a statistically significant difference between CCBs and beta-blockers. Based on the results of one study (ASCOT),[22] CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.71, 95% CI 0.64 to 0.78). ASCOT[22] also found CCBs to be associated with a lower incidence of unstable angina (HR 0.68, 95% CI 0.51 to 0.92) and fewer revascularisation procedures (HR 0.86, 95% CI 0.77 to 0.96) than BBs, but the INVEST[32] study found the association between both classes of drugs to be non-significant for these outcomes. Study withdrawal was reported in two studies. In ASCOT[22] there were fewer withdrawals associated with CCBs (RR 0.64, 95% CI 0.52 to 0.77), but in INVEST[32] there was no significant difference.	II
Calcium-channel blockers versus thiazide-type diuretics	
A meta-analysis of five studies (ALLHAT,[11–13] INSIGHT,[30,31] MIDAS,[33] NICS-EH,[36] VHAS[41,42]) comparing calcium-channel blockers with thiazide-type diuretics found no significant differences for mortality, MI or stroke. There was a statistically significantly higher incidence of heart failure with CCBs (RR 1.38, 95% CI 1.25 to 1.53). Conversely, based on the results of three studies (ALLHAT,[11–13], INSIGHT,[30,31] NICS-EH[36]), CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.78, 95% CI 0.64 to 0.96).	I
Only the ALLHAT[11–13] study reported unstable angina as an outcome and found no significant difference between the drug classes. For revascularisation procedures, neither ALLHAT[11–13] nor MIDAS[33] found a significant difference. In terms of study drug withdrawal, one study (INSIGHT)[30,31] found thiazide-type diuretics to be associated with more withdrawals than CCBs (RR 1.20, 95% CI 1.13 to 1.28), although the other studies (ALLHAT,[11–13] MIDAS,[33] VHAS[41,42]) did not find a significant difference between the two drug classes.	II
Outcomes in those with isolated systolic hypertension (ISH)	
A meta-analysis of three randomised controlled trials (SHEP,[4–7] SHEP-P,[8–10] SYST-EUR[1–3]) compared active antihypertensive drug therapy using either thiazide-based diuretics or a calcium-channel blocker with placebo in patients with isolated systolic hypertension. Antihypertensive drug therapy was associated with a reduced incidence of stroke (OR 0.62, 95% CI 0.51 to 0.77) and myocardial infarction (OR 0.74, 95% CI 0.61 to 0.91), although there was no statistically significant difference in mortality rate.	I
Based on the results of a subgroup analysis from one randomised controlled trial (INSIGHT),[30,31] initial antihypertensive therapy with the CCB nifedipine was comparable to the thiazide-type diuretic hydrochlorothiazide plus amiloride in terms of mortality.	II

continued

Outcomes in those with isolated systolic hypertension (ISH) – *continued*	Level
Based on the results of another subgroup analysis of patients with ISH from a randomised-controlled trial involving patients with hypertensive LVH (LIFE)[52], initial therapy with an ARB is associated with a reduced incidence of stroke (RR 0.60, 95% CI 0.38 to 0.92) and a lower mortality rate (RR 0.54, 95% CI 0.34 to 0.87) compared to initial antihypertensive therapy with a beta-blocker. The two drugs were comparable in terms of the incidence of myocardial infarction.	
Outcomes in black patients with hypertension	
Based on the results of a subgroup analysis comprising black patients from one randomised controlled trial (ALLHAT),[11–13] initial antihypertensive therapy with the ACE inhibitor lisinopril was associated with a higher incidence of stroke (RR 1.40, 95% CI 1.17 to 1.68) and cardiovascular events (RR 1.19, 95% CI 1.09 to 1.30) compared to the thiazide-type diuretic chlorthalidone. There was no significant difference in terms of mortality. Based on analysis of the same subgroup, initial antihypertensive therapy with the thiazide-type diuretic chlorthalidone is comparable to initial antihypertensive therapy with the CCB amlodipine in terms of the incidence of myocardial infarction combined with coronary heart disease, stroke, cardiovascular events and mortality. A subgroup analysis comprising black patients with hypertension and LVH from another randomised controlled trial (LIFE)[53] showed that treatment with the ARB losartan was associated with a higher incidence of stroke compared with the beta-blocker atenolol (HR 2.18, 95% CI 1.08 to 4.40). There was no statistically significant difference in myocardial infarction or mortality.	**II**
Outcomes in younger patients	
The literature search found no evidence for the clinical outcomes summarised above, therefore blood pressure response to drug therapy was used as a surrogate. Three studies[54–56] and an age-stratified analysis from a fourth study[57] 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. In older people, initial treatment with calcium channel-blockers or thiazide-type diuretics has been shown to be more effective at blood pressure lowering than ACE inhibitors, angiotensin-II receptor antagonists or beta-blockers.[11–13,22,26]	

1.2.3 Meta-analysis results summary

Table 2 summarises the results from the meta-analysis comparing different drug classes in general antihypertensive populations. Included are comparisons and outcomes in which inter-study heterogeneity was considered too great to include the pooled effect size in the evidence statements above and hence these should be treated with caution.

Table 2 Summary of effect sizes for each comparison included in the meta-analysis

Comparison	Studies	Total n	Effect size RR [95% CI]	I^2 (%)
01 Beta-blockers versus thiazides				
01 Mortality	3	15,765	1.04 [0.91, 1.20]	44.1
02 Myocardial infarction	3	15,765	1.15 [0.82, 1.60]	76.8
03 Stroke	3	15,765	1.27 [0.73, 2.23]	77.6
04 ACE inhibitors versus calcium-channel blockers				
01 Mortality	3	23,625	1.04 [0.98, 1.11]	0
02 Myocardial infarction	3	23,619	0.94 [0.74, 1.19]	69.3
03 Stroke	3	23,619	1.15 [1.03, 1.27]	5.2
04 Heart failure	3	23,619	0.85 [0.78, 0.93]	0
05 Diabetes	2	15,501	0.85 [0.76, 0.94]	15.2
03 ARBs versus beta-blockers				
01 Mortality	1	9,103	0.89 [0.78, 1.01]	N/A
02 Myocardial infarction	1	9,103	1.05 [0.86, 1.28]	N/A
03 Stroke	1	9,103	0.75 [0.63, 0.88]	N/A
04 Heart failure	1	9,103	0.95 [0.76, 1.18]	N/A
05 Diabetes	1	7,998	0.75 [0.64, 0.88]	N/A
02 ARBs versus calcium-channel blockers				
01 Mortality	1	15,313	1.02 [0.93, 1.12]	N/A
02 Myocardial infarction	1	15,313	1.17 [1.01, 1.36]	N/A
02 Stroke	1	15,313	1.14 [0.97, 1.33]	N/A
03 Heart failure	1	15,313	0.88 [0.76, 1.01]	N/A
05 ACE inhibitors versus thiazides				
01 Mortality	2	29,697	1.00 [0.94, 1.06]	0%
02 Myocardial infarction	3	30,204	0.87 [0.60, 1.24]	66.5
03 Stroke	3	30,204	1.13 [1.02, 1.25]	0
04 Heart failure	2	29,697	1.07 [0.81, 1.41]	67.1

continued

Table 2 Summary of effect sizes for each comparison included in the meta-analysis – *continued*

06 Calcium-channel blockers versus beta-blockers				
01 Mortality	3	44,075	0.94 [0.88, 1.00]	5.7
02 Myocardial infarction (inc. silent MI)	3	44,075	0.93 [0.83, 1.03]	0
03 Myocardial infarction (exc. silent MI)	3	44,075	0.91 [0.81, 1.02]	0
04 Stroke	2	21,499	0.77 [0.67, 0.88]	0
05 Heart failure	2	41,833	0.96 [0.74, 1.26]	67.4
06 Diabetes	1	14,112	0.71 [0.64, 0.78]	N/A
07 Calcium-channel blockers versus thiazides				
01 Mortality	5	32,195	0.97 [0.93, 1.02]	0
02 Myocardial infarction	5	32,195	1.02 [0.96, 1.08]	0
03 Stroke	5	32,195	0.93 [0.84, 1.04]	0
04 Heart failure	5	32,195	1.38 [1.25, 1.53]	0.2
05 Diabetes	3	20,885	0.82 [0.75, 0.90]	43.8
08 Antihypertensive therapy versus placebo (ISH population)				
01 Mortality	3	9,745	0.88 [0.77, 1.01]	0
02 Myocardial infarction	3	9,745	0.75 [0.62, 0.91]	0
03 Stroke	3	9,745	0.64 [0.52, 0.78]	0

1.3 Health economic model

The GDG drafted recommendations on the basis of the clinical evidence shown above. A health economic analysis was then conducted to balance the clinical outcomes and to test the cost effectiveness of different initial antihypertensive medications. The results of this analysis supported the preliminary clinical conclusions.

1.3.1 Methodological introduction

- Economic question

The aim of the model was to estimate the cost effectiveness of the various blood pressure lowering drug classes for the management of hypertension in primary care.

- Population and subgroups

The model considered patients with essential hypertension seen in primary care, excluding those with pre-existing cardiovascular disease (CVD), heart failure (HF) or diabetes. It was

designed to be run separately for different cohorts, defined by age (55, 65, 75 and 85) and sex. In addition, the model classified these cohorts by baseline CVD risk (0.5%–5% per year), by heart failure risk (0–5% per year) and by diabetes risk (0–5% per year). A base case analysis was performed for 65-year-old men and women with 2% CVD risk, 1% HF risk and 1.1% diabetes risk, and a sensitivity analysis considered the effect of varying these risk levels.

The trial evidence that the model is based on included relatively few younger (under 55) or black patients, so the results may not be reliable for these groups. However, we did conduct sensitivity analyses to explore how different assumptions about treatment effects might impact on the cost-effectiveness results for younger (45) and black patients (people from Black African and Black Caribbean ethnic groups).

Interventions compared

The analysis assessed the costs and effects of the various classes of blood pressure-lowering drugs alongside a 'do nothing' comparator. Inclusion of no treatment as an option is important for economic evaluations as it allows us to identify low-risk groups for whom treatment is not likely to be cost effective.

The interventions compared were thus:

- no intervention (NI)
- thiazide-type diuretics (D)
- calcium-channel blockers (C)
- beta-blockers (B)
- ACE inhibitors/angiotensin II receptor antagonists (ARBs) (A).

It was assumed that 80% of patients starting on ACE inhibitors would continue with these, but that 20% would switch to ARBs due to an inability to tolerate ACE inhibitors (expert opinion). The costs and effects of the drugs were weighted to take account of this.

For simplicity only first-line drugs were considered. However, it should be noted that the relative treatment effects from the meta-analysis include additional benefits from various second and third line treatments offered in the trials.

Outcomes

The treatment effects were measured in terms of prevention of CVD events (non-fatal unstable angina, MI, heart failure and stroke) and CVD-related deaths. The only adverse effects modelled were onset of HF and diabetes, although we did examine the possible impact of other adverse reactions to the drugs in sensitivity analyses.

It should also be noted that the model does not explicitly include cost impacts of withdrawals, non-concordance or transfers between treatments. The impact of such changes on effectiveness is implicitly included through the use of intention-to-treat trial data.

Health outcomes for the cost-effectiveness analysis are summarised in the form of quality adjusted life years (QALYs), where one QALY represents one year of healthy life.

▷ Cost-effectiveness

The results of cost-effectiveness analysis are usually presented as incremental cost-effectiveness ratios (ICERs), which determine the additional cost of using one drug (X) per additional QALY gained, compared with no intervention or another drug (Y):

ICERs = (cost of X – cost of Y)/(QALY of X – QALY of Y)

Where more than two interventions are being compared, the ICERs are calculated using the following process.

- The drugs are ranked in terms of cost (from the cheapest to the most expensive).
- If a drug is more expensive and less effective than the previous one, then it is said to be 'dominated' and is excluded from further analysis.
- ICERs are then calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next most effective strategy, then it is ruled out by 'extended dominance'.
- ICERs are recalculated excluding any drugs subject to extended dominance.

It is important to bear in mind that comparison between the crude cost-effectiveness ratios for two drugs each compared with 'no intervention' can be highly misleading. To illustrate, the incremental cost of starting antihypertensive therapy with the cheapest drug is relatively low, while the incremental benefit is high, and thus the ICER is small. A more expensive but more effective drug may also appear to have a relatively small cost-effectiveness ratio when compared with 'no treatment'. However, the more expensive drug may have a larger ICER when it is compared with the cheaper drug – the incremental cost of switching from the cheaper drug to the more expensive one may be quite large in relation to the incremental health gain. Nevertheless, the more expensive drug may still be a *cost-effective* alternative to the cheaper drug if its ICER is less than the maximum amount that we are prepared to pay for a QALY, which is considered to be around £20,000 to £30,000 for NICE decisions. In this situation the most cost-effective option is the more expensive drug, despite its larger ICER. However, if the ICER for the more expensive drug were to exceed the threshold of £20 to 30,000 per QALY, then it would not be cost effective and the cheaper option should be preferred.

1.3.2 Results of the health economic model

▷ Base case results

The base case results are presented in Table 3 for 65-year-old men and women with an annual CVD risk of 2%, HF risk of 1% and diabetes risk of 1.1%. This analysis suggests that antihypertensive treatment is cost effective for this population and that the most cost-effective initial drug in this group is calcium channel blockers (C). The ICER of C compared with thiazide-type diuretics (D) is about £12,000 to £13,000 per QALY gained, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Beta-blockers (B) are ruled out by simple dominance, since D is estimated to be cheaper and more effective. This can be seen in Figure 1, since B lies to the northwest of D. The ACEi/ARB option (A) is also ruled out by extended dominance, since treating some patients with D and the remainder with C would be cheaper and more effective than A: in Figure 1, A lies to the northwest of a straight line joining points D and C. However, it should be noted that the absolute difference between A and C is small.

The results of this analysis are set out in more detail, together with the sensitivity analyses, in Appendix B.

Table 3 Base case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% HF risk)

Men			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,360	10.12	–
NI	£4,390	9.49	–
B	£4,530	9.80	–
A	£5,020	10.15	–
C	£5,110	10.19	£12,250
Women			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,670	10.55	–
NI	£4,740	9.87	–
B	£4,870	10.20	–
A	£5,340	10.57	–
C	£5,430	10.61	£13,490

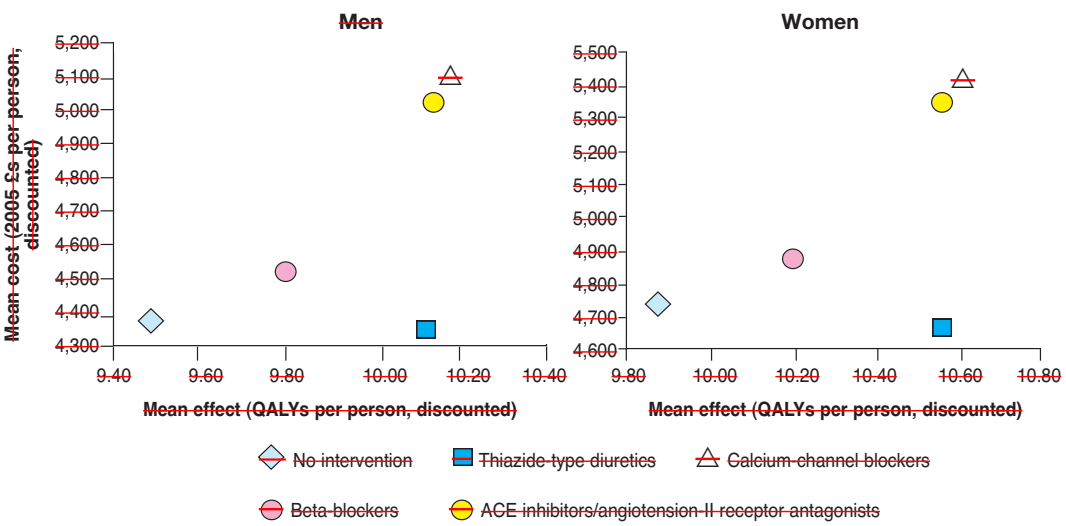

Figure 1 Base case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% HF risk)

1.3.3 Conclusions

The trials on which the cost-effectiveness calculations are based did not, in general, show large differences in clinical outcomes between drug classes. Some of the outcomes have point estimates of effect that are not statistically significant. In these situations the point estimate is used as the best estimate of effect and so effects that are not statistically significant have a bearing on the relative cost effectiveness. Where the outcomes have a large effect on quality of life or cost (for example, stroke or death) the effect on overall cost effectiveness may be relatively important. The GDG considered the effect of this uncertainty about important outcomes in reaching their conclusions. The relative cost effectiveness of the agents also depend on the propensity of patients treated with them to develop new-onset diabetes or heart failure. The GDG were aware that both of these adverse outcomes should be treated with some caution in this context. It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances, and the same applies to heart failure diagnoses, particularly since the definition of this outcome in some studies would not satisfy currently accepted criteria.

Nevertheless, allowing for these caveats, the cost effectiveness analysis is supportive of the conclusions which the GDG had already reached from their consideration of the clinical data in that beta-blockers are the class of drug least favoured, and CCBs and thiazide-type diuretics appear the most cost-effective choices in most scenarios.

The applicability of the model to people under the age of 55 is uncertain, since it is based on trial data from mostly older people. However, sensitivity analysis showed that the drugs that affect the renin-angiotensin system are likely to be the most cost-effective option in this group if they are even slightly more effective in the young than is suggested from the overall trial data.

These results are sensitive to the cost of CCBs. The more expensive brands are not likely to be cost effective for use in the NHS. For example, the model estimates that for 65-year-olds at 2% annual CVD risk, 1.1% diabetes risk and 1% heart failure risk CCBs are only cost effective if they cost less than £105 per patient per year.

Finally, it should be emphasised that there is still considerable uncertainty about the size of some treatment effects, which translates into uncertainty about the relative cost-effectiveness of the drugs. The evidence base is also difficult to interpret because of the complex nature of some of the treatment protocols and also because of differences in some of the trial populations.

1.4 From evidence to recommendations

As described in the evidence statements above, a number of large studies which had not been published in time for consideration in the 2004 NICE guideline have now become available. These were appraised and the data considered together with those from the earlier studies, using meta-analysis where appropriate. In formulating their recommendations, the Guideline Development Group (GDG) gave due primacy to this evidence, but other factors were taken into account. Adverse events data and issues of patient concordance were particularly noted and the group also had access to a detailed health economic analysis comparing the cost effectiveness of the main drug classes, something that had not been available to the original

NICE guideline group. Consideration was also given to the pathogenesis of hypertension and the mechanism of action of the different classes of blood pressure lowering drugs allowing for age and ethnicity. In particular, the GDG considered evidence suggesting that a patient's age and ethnicity influences their renin status,[58] and thus the blood pressure lowering response to the initial drug therapy.[54-56,59-61] Finally, where the evidence did not prove definitive, the group took into account existing guidelines and constructed recommendations most compatible with current good practice. It was reasoned that this would enhance acceptability of the new recommendations among patients and clinicians.

In formulating their recommendations, the GDG have assumed a 'drug class effect' when assessing results of studies using any particular pharmacological agent, unless there was clear evidence to the contrary. However, it should be noted that clinical outcome trials involving thiazide type diuretics have used a variety of different drugs under this class heading and at different doses. There is still uncertainty about drug and dose equivalence across this class and the GDG noted that there remains a paucity of evidence from outcome trials with bendroflumethiazide at the dose most commonly used for initial therapy in the UK (2.5 mg once daily). Nevertheless, drug and dose equivalence with the lower dose thiazide type diuretics used in the trials has been assumed for the purposes of the analyses. Moreover, the GDG felt that the benefit from ACE inhibitors and angiotensin II receptor antagonists were closely correlated and that they should be treated as equal in terms of efficacy (although due to cost differences, ACE inhibitors should be initiated first).

One class which caused particular debate was the beta-blockers. The GDG noted that in head-to-head trials, beta-blockers were usually less effective than the comparator drug at reducing major cardiovascular events, in particular stroke. Atenolol was the beta-blocker used in most of these studies and, in the absence of substantial data with other agents, it is unclear whether this conclusion applies to all beta-blockers. However, if atenolol studies are excluded, the total evidence on the use of beta-blockers for the treatment of hypertension is much less than for the other main drug classes. It was therefore concluded that in the absence of other compelling indications for beta-blockade (for example, angina), beta-blockers should not be a preferred initial treatment for hypertension.

The GDG noted that in most studies, a significant number of patients had required treatment with multiple agents in order to achieve blood pressure control, irrespective of the nominal comparator agents. This adds to the difficulty of study interpretation. However, allowing for this the GDG felt that the evidence showed calcium-channel blockers (CCB) or thiazide-type diuretics to be the most likely drugs to confer benefit as first-line treatment for most patients. The health economic model slightly favoured CCBs with thiazide-type diuretics as the next most cost-effective option, although there is some uncertainty around this conclusion. This reflects the influence of estimates for important outcomes that are not statistically significant. Given the potential limitations of the model, the GDG decided after debate that CCBs and thiazide-type diuretics should be offered as equal alternatives for clinicians to consider as first-line treatment.

The choice between thiazide-type diuretics and CCBs should be made by the clinician and patient using careful clinical judgement about the patient's risk of adverse effects and consideration of the patient's preferences.

This conclusion becomes less certain for younger patients (defined for the purpose of this guideline update as under 55 years). This group have been poorly represented in clinical trials because being aged 55 or over has been used as an inclusion criterion for many trials. In the absence of clinical outcomes data in younger patients, the GDG considered that for pragmatic reasons it was essential to make a recommendation and considered blood pressure lowering as the most suitable surrogate for clinical outcomes. There are data suggesting that the blood pressure lowering response in older patients is greatest when initial therapy is with a CCB or a thiazide-type diuretic. However, there are more limited data examining blood pressure lowering efficacy in younger patients. This evidence suggests that initial therapy with a beta-blocker or an ACE-inhibitor (or angiotensin-II receptor antagonist) may provide superior initial blood pressure lowering when compared with a CCB or thiazide-type diuretic. The studies suggesting beta-blockers are generally an inferior choice have already been covered. Consequently, the GDG concluded that the best resolution of this data is to recommend that below the age of 55 an ACEi (or an ARB if an ACEi is not tolerated) is the preferred choice as initial therapy.

There was little evidence directly addressing drug combinations if blood pressure is not controlled with initial therapy, although in practice combinations were frequently used in the study populations. Many patients will require more than one drug to achieve adequate blood pressure control. Pathophysiological reasoning suggests that adding an ACE inhibitor to a CCB or a diuretic (or vice versa in the younger group) are logical combinations, ie A+C or A+D. In addition, these combinations have been commonly used at step 2 in the clinical trials.

Beyond this point there is even less evidence to guide practice but the group concluded that the most straightforward choice is to recommend combining the three drug classes which have been employed at steps 1 and 2, a three-drug combination of ACE inhibitor (or ARB) + CCB + diuretic, ie A+C+D.

The widely used class of drug which is omitted from this regimen is the beta blocker. The evidence overall suggests that clinical benefit is least likely (especially for stroke prevention) with these agents. However, given the relative lack of clinical outcome data from trials of treating hypertension with beta-blockers other than atenolol, concern about the generalisability of this conclusion, beyond atenolol, to all beta-blockers remains. The GDG felt that good studies with alternative beta-blockers in people with hypertension are required for this conclusion to be reversed. An additional concern is the increased risk of developing diabetes, particularly with the combination of a beta-blocker with a thiazide-type diuretic. Omitting beta-blockers from the routine treatment algorithm was therefore justified. Nevertheless, the GDG noted that there are certain compelling indications for beta-blockers which have been specified.

It follows that recommendations beyond a three-drug combination are based on consensus rather than hard evidence, and indeed the GDG debated whether they were justified in proceeding to this stage. However, it was felt that practitioners would appreciate some guidance. Potentially useful strategies may be to add additional diuretic therapy, either by increasing the dose of the thiazide-type diuretic or considering the addition of alternative diuretic therapy such as spironolactone or amiloride, although patients on these agents require more careful monitoring of their renal function and electrolytes. Alternatively, a selective alpha-blocker or beta-blocker might be considered at this stage. The GDG also felt that if three drugs in combination were failing to provide adequate blood pressure control, a practitioner might consider seeking expert advice. If blood pressure is not controlled despite the use of four drugs, a practitioner should consider seeking expert advice.

1.5 RECOMMENDATIONS

These should be read in conjunction with the algorithm on page 19 (Figure 2).

R1 In hypertensive patients aged 55 or over, or black* patients of any age, the first choice for initial therapy should be either a calcium-channel blocker or a thiazide-type diuretic. **A**

~~**R2** In hypertensive patients younger than 55, the first choice for initial therapy should be an ACE inhibitor**.~~ ~~**C**~~

~~**R3** If initial therapy was with a calcium-channel blocker or a thiazide-type diuretic and a second drug is required, add an ACE inhibitor*. If initial therapy was with an ACE inhibitor*, add a calcium-channel blocker or a thiazide-type diuretic.~~ ~~**B**~~

R4 If treatment with three drugs is required, the combination of ACE inhibitor**, calcium-channel blocker and thiazide-type diuretic should be used. **B**

R5 If blood pressure remains uncontrolled on adequate doses of three drugs, consider adding a fourth and/or seeking expert advice. **C**

~~**R6** If a fourth drug is required, one of the following should be considered:~~ ~~**C**~~

- ~~a higher dose of a thiazide-type diuretic or the addition of another diuretic (careful monitoring is recommended) or~~
- ~~beta-blockers or~~
- ~~selective alpha-blockers.~~

R7 If blood pressure remains uncontrolled on adequate doses of four drugs and expert advice has not yet been obtained, this should now be sought. **C**

R8 Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly: **B**

- those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists or
- women of child-bearing potential or
- patients with evidence of increased sympathetic drive.

In these circumstances, if therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-type diuretic to reduce the patient's risk of developing diabetes. **C**

R9 In patients whose blood pressure is not controlled (ie over 140/90 mmHg) despite a treatment regimen including a beta-blocker, treatment should be revised according to the treatment algorithm (see Figure 2). **C**

R10 In patients whose blood pressure is well-controlled (ie 140/90 mmHg or lower) with a regimen which includes a beta-blocker, long-term management should be considered as part of their routine review. In these patients, there is no absolute need to replace the beta-blocker with an alternative agent. **C**

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*Including both Black African and Black Caribbean patients, not Asian, Chinese, mixed-race, or other ethnic groups.

**Or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated.

R11 When a beta-blocker is withdrawn, the dose should be stepped down gradually. Beta-blockers should not be withdrawn in patients with compelling indications for beta-blockade, for example those who have symptomatic angina or who have had a myocardial infarction. **C**

1.6 Recommendations that are not changing

The GDG is not proposing to change the following recommendations from section 1.4 of the original NICE clinical guideline on hypertension in primary care (CG 18). These recommendations will still apply after publication of the updated guideline, and are not part of the consultation.

~~1.4.1 Drug therapy reduces the risk of cardiovascular disease and death. Offer drug therapy to:~~ ~~A~~

- ~~patients with persistent high blood pressure of 160/100 mmHg or more~~
- ~~patients at raised cardiovascular risk (10-year risk of CVD ≥20% or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.~~

1.4.2 Provide appropriate guidance and materials about the benefits of drugs and the unwanted side effects sometimes experienced in order to help patients make informed choices. **D**

1.4.3 Offer drug therapy, adding different drugs if necessary, to achieve a target of 140/90 mmHg, or until further treatment is inappropriate or declined. Titrate drug doses as described in the British National Formulary noting any cautions and contraindications. **A**

1.4.10 Offer patients with isolated systolic hypertension (systolic BP >160 mmHg) the same treatment as patients with both raised systolic and diastolic blood pressure. **A**

1.4.11 Offer patients over 80 years of age the same treatment as other patients over 55, taking account of any comorbidity and their existing burden of drug use. **A**

1.4.12 Where possible, recommend treatment with drugs taken only once a day. **A**

1.4.13 Prescribe non-proprietary drugs where these are appropriate and minimise cost. **B**

NICE clinical guideline 18 was developed by the Newcastle Guideline Development and Research Unit. It is available from **www.nice.org.uk/CG018**

1.7 Algorithm: treatment of newly diagnosed hypertension

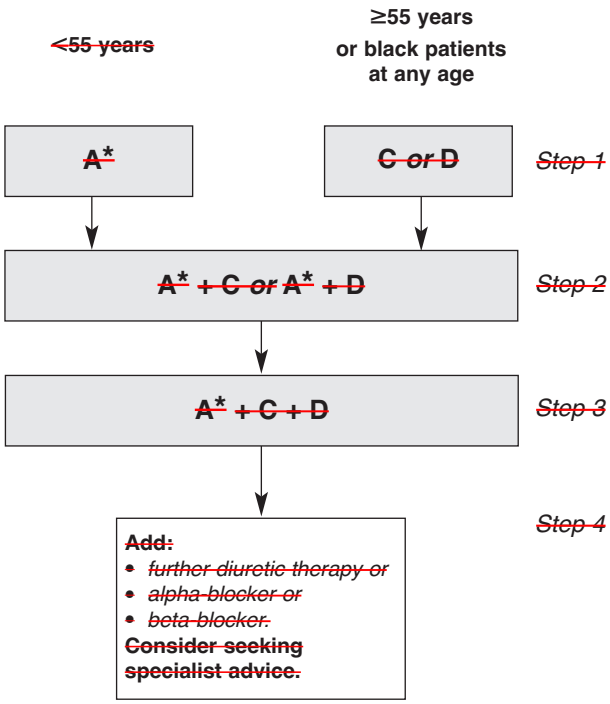


Figure 2 Algorithm. A = ACE inhibitor (* or ARB if ACEi-intolerant); C = calcium-channel blocker; D = thiazide-type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black.

BHS
British Hypertension Society

Royal College of Physicians
Setting higher medical standards

2 Glossary

Adverse events	A harmful, and usually relatively rare, event arising from treatment.
Algorithm (in guidelines)	A flowchart of the clinical decision pathway described in the guideline.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT, and potential bias that may result.
Audit	See 'clinical audit'.
Bias	The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.
Blinding (masking)	A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions which have been allocated.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.
Class of recommendation	All recommendations are assigned a class (A, B, C) according to the level of evidence the recommendation is based on (see 'level of evidence').
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinician	In this guideline, the term clinician means any healthcare professional.
Cochrane review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Concordance	Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.
Confidence interval (CI)	A range of values which contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence interval means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Discounting	The process of converting the cost or benefits to be incurred or received at different points in the future to a present value so that they can be compared in commensurate units as if they all occur at the same point in time.
Dominance	A situation where an intervention is more effective clinically and less costly than its comparator.
Evidence-based healthcare	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Extended dominance	A situation where treating patients with a combination of two drugs is estimated to be cheaper and more effective than using one drug.
Fixed effects model	A mathematical model that can be used in meta-analyses to calculate a pooled estimate of the effect size. It assumes that each trial is reporting an estimate of a single underlying 'fixed' effect size.
Follow-up	An attempt to measure the outcomes of an intervention after the intervention has ended.
Generalisability	The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.
Grade of recommendation	See 'class of recommendation'.
Guideline Development Group (GDG)	An independent group set up on behalf of NICE to develop a guideline. They include healthcare professionals and patient and carer representatives.
Hazard ratio (HR)	A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.

Heterogeneity	In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.
Homogeneity	In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.
Inclusion criteria	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The cost of one alternative less the cost of another.
Incremental cost-effectiveness ratio (ICER)	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Level of evidence	A code (eg I, II) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.
Methodological limitations	Features of the design or reporting of a clinical study, which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
National Collaborating Centre for Chronic Conditions (NCC-CC)	A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the NICE Patient & Public Involvement Programme, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient Involvement Unit, the Royal College of Surgeons of England and the Royal Pharmaceutical Society of Great Britain. Set up in 2001 to undertake commissions from NICE to develop clinical guidelines for the NHS.
National Health Service (NHS)	This guideline is written for the NHS in England and Wales.

National Institute for Health and Clinical Excellence (NICE)	NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.
Outcome	Measure of the possible results that may stem from exposure to prevention or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints.
p-values	The probability that an observed difference could have occurred by chance. A p-value of less than 0.05 is conventionally considered to be 'statistically significant'.
Placebo	An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.
Quality of life	Refers to the level of comfort, enjoyment and ability to pursue daily activities.
Quality-adjusted life year (QALY)	A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.
Random effects model	A mathematical model that can be used in meta-analyses to calculate a pooled estimate of the effect size. In contrast to a fixed effects model, it assumes that each trial contributes its own underlying effect, independently of the others. This is a useful approach when dealing with heterogeneous trials.
Randomisation	Allocation of participants in a study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

Relative risk (RR)	An estimate for the number of times more likely or less likely an event is to happen in one group of people compared with another, based on the incidence of the event in the intervention arm of a study, divided by the incidence in the control arm.
Sample size	The number of participants included in a trial or intervention group.
Sensitivity analysis	A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.
Single blind study	A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.
Specialist	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
Stakeholder	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
Statistical power	In clinical trials, the probability of correctly detecting an underlying difference of a pre-specified size due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being correctly detected as statistically significant, though they may not be clinically significant.
Statistical significance	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Withdrawal	When a trial participant discontinues the assigned intervention before completion of the study.

3 Search strategy

Table 6 Search strategy

Question ID	Question wording	Study type filters used	Databases and years
PHAR 1	In patients with essential hypertension, what is the efficacy and tolerability of different classes of antihypertensive drugs in preventing death, vascular events and diabetes?	RCTs	Medline 2004–2005 Embase 2004–2005

4 Summaries of product characteristics

At the time of publication of this pharmacological guideline update, not all the drugs in the classes recommended for use have UK marketing authorisation for hypertension. Check the Summaries of Product Characteristics for current licensed indications. Medicines may be used for indications not covered by the UK marketing authorisation if this is justified by a responsible body of professional opinion and informed consent is obtained.

5 Research recommendations

1. The clinical and cost effectiveness of antihypertensive therapies in people aged below 55 years.
2. The clinical effectiveness of antihypertensive therapies in minority ethnic groups, particularly black and Asian people.
3. The adoption of quality of life measures within future clinical trial protocols of antihypertensive therapy to allow measures of drug class utility.
4. The most effective treatment of hypertension resistant to therapy with three blood pressure lowering drugs.

6 Audit criteria

Percentage of patients newly diagnosed with essential hypertension who are offered drug therapy, who either:

- have persistent high blood pressure of 160/100 mmHg or more, or
- are at raised cardiovascular risk (10-year risk of CVD more than or equal to 20% or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.

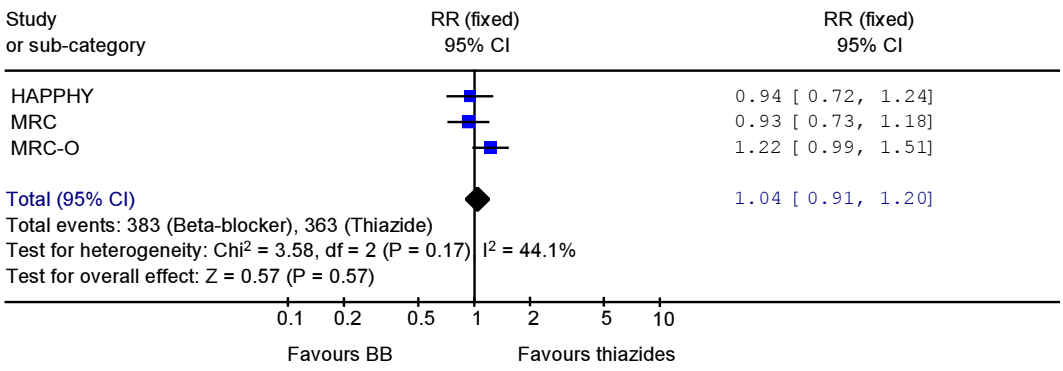
Percentage of patients newly diagnosed with essential hypertension who are aged 55 or over, or black (any age), offered a calcium-channel blocker or a thiazide-type diuretic as the first choice for initial drug therapy.

Appendix A: Forest plots

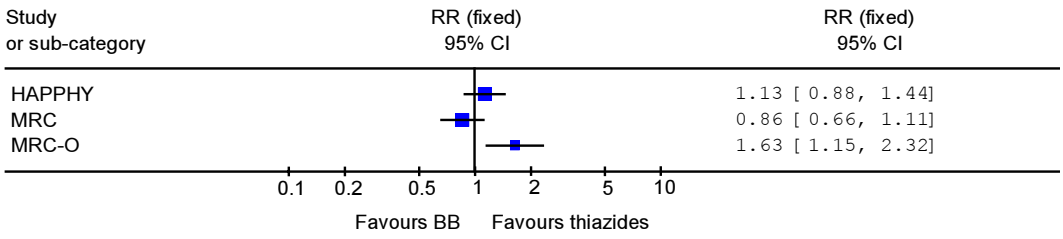
The final cut-off date for all searches was 19 December 2005.

The following abbreviations were used: ACEi = angiotensin-converting inhibitors; ARB = angiotensin II receptor antagonists; BB = beta blockers; CCB = calcium channel blockers; CI = confidence interval; MI = myocardial infarction; RR = relative risk.

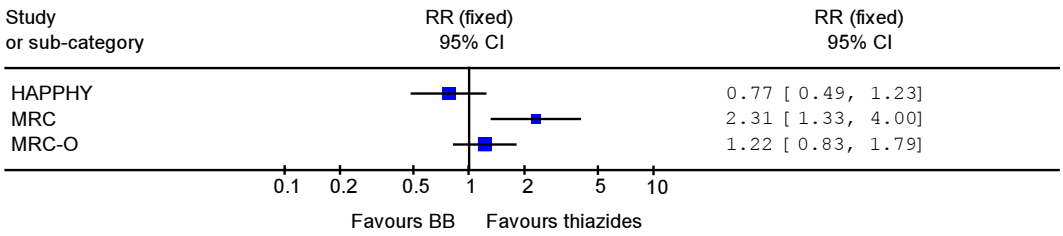
Comparison: 01 Beta-blockers versus thiazides
Outcome: 01 Mortality



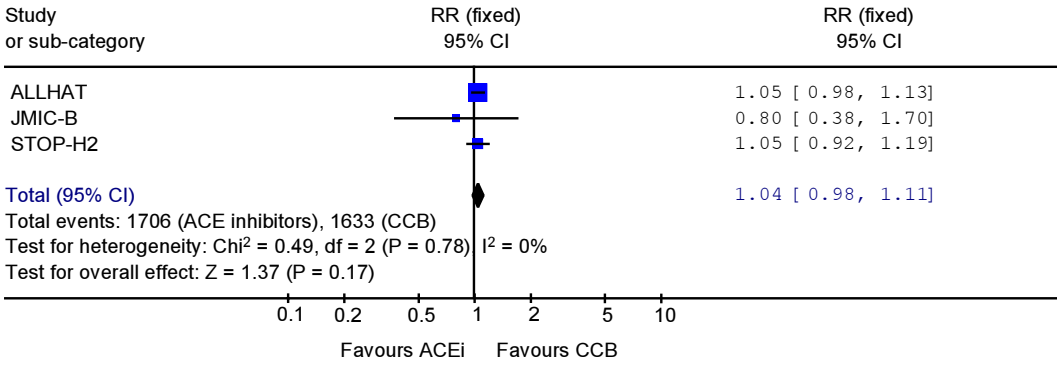
Comparison: 01 Beta-blockers versus thiazides
Outcome: 02 Myocardial infarction



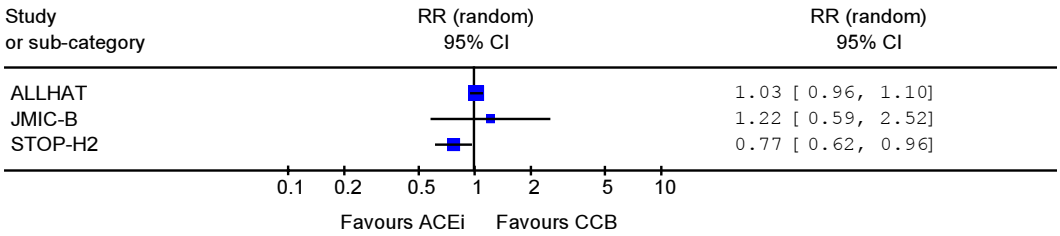
Comparison: 01 Beta-blockers versus thiazides
Outcome: 03 Stroke



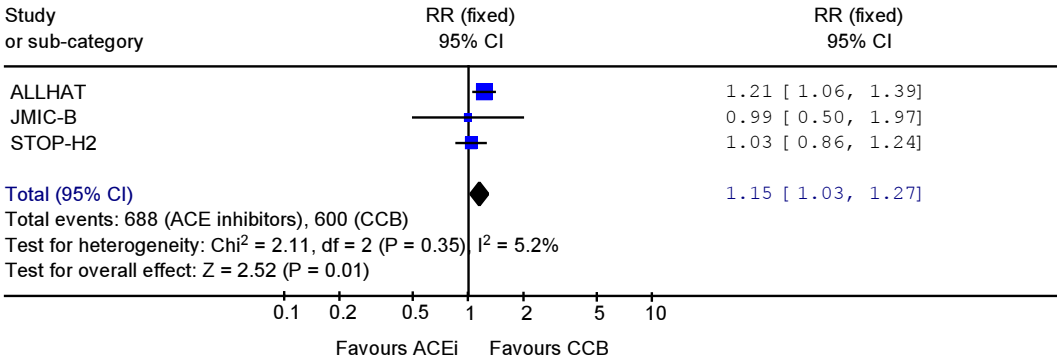
Comparison: 04 ACE inhibitors versus calcium-channel blockers
Outcome: 01 Mortality



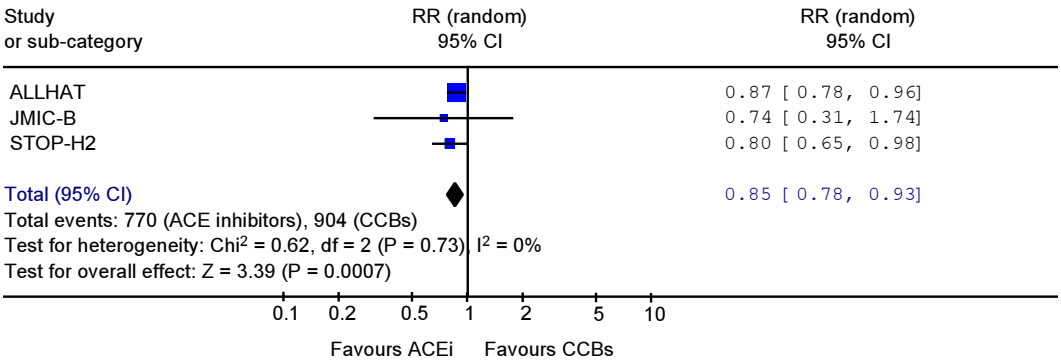
Comparison: 04 ACE inhibitors versus calcium-channel blockers
Outcome: 02 Myocardial infarction



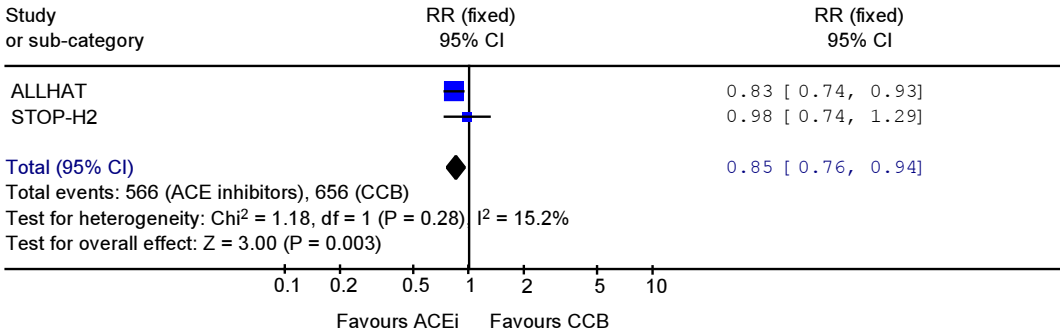
Comparison: 04 ACE inhibitors versus calcium-channel blockers
Outcome: 03 Stroke



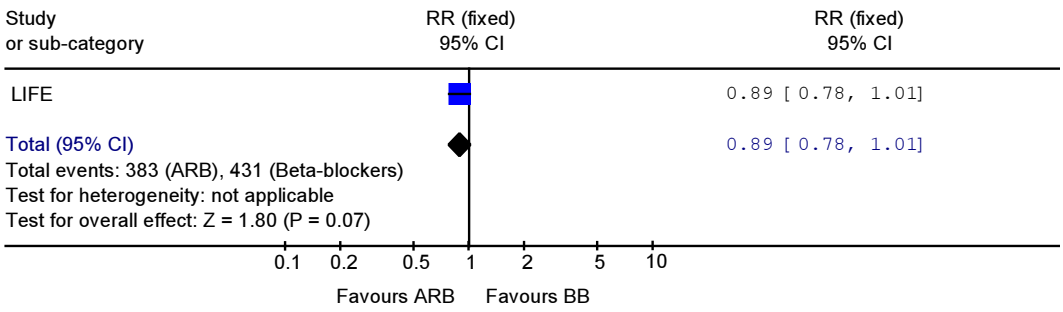
Comparison: 04 ACE inhibitors versus calcium-channel blockers
Outcome: 05 Heart failure



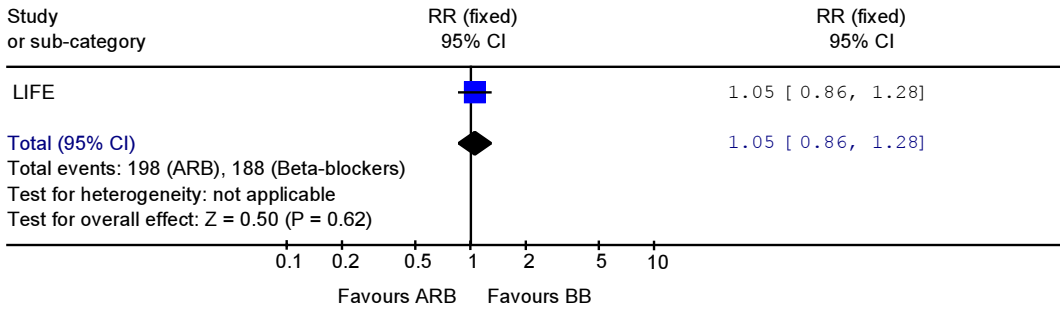
Comparison: **04 ACE inhibitors versus calcium-channel blockers**
Outcome: **05 Diabetes**



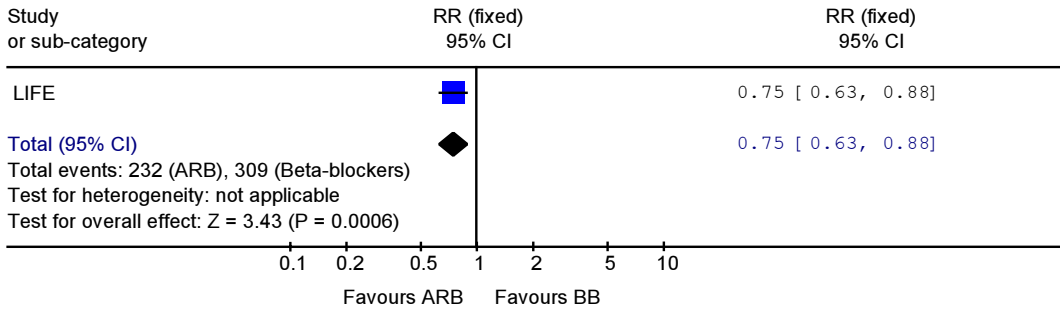
Comparison: **03 ARBs versus beta-blockers**
Outcome: **01 Mortality**



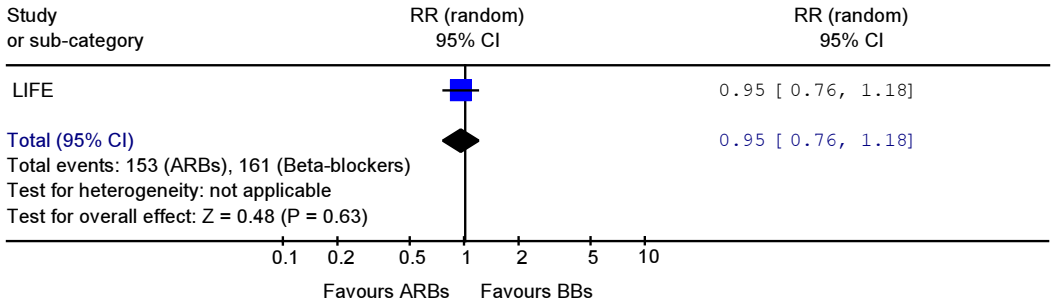
Comparison: **03 ARBs versus beta-blockers**
Outcome: **02 Myocardial infarction**



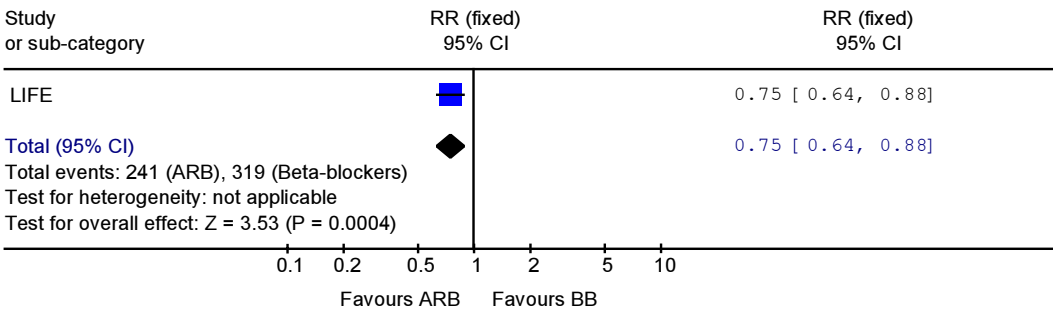
Comparison: **03 ARBs versus beta-blockers**
Outcome: **03 Stroke**



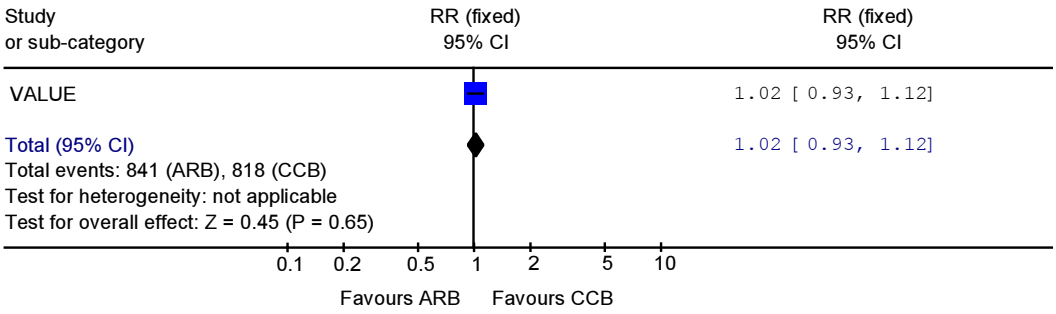
Comparison: **05 ARBs versus beta-blockers**
Outcome: **05 Heart failure**



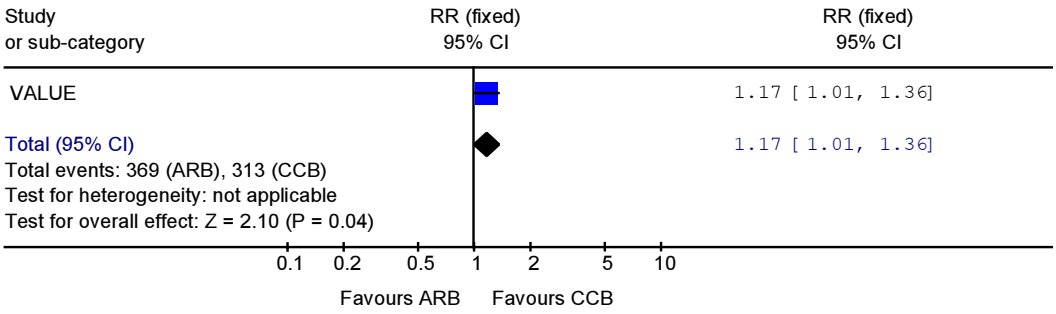
Comparison: **03 ARBs versus beta-blockers**
Outcome: **05 Diabetes**



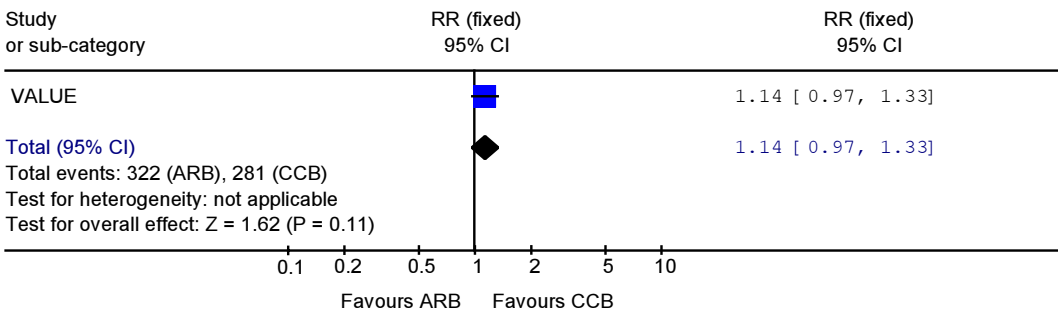
Comparison: **02 ARBs versus calcium-channel blockers**
Outcome: **01 Mortality**



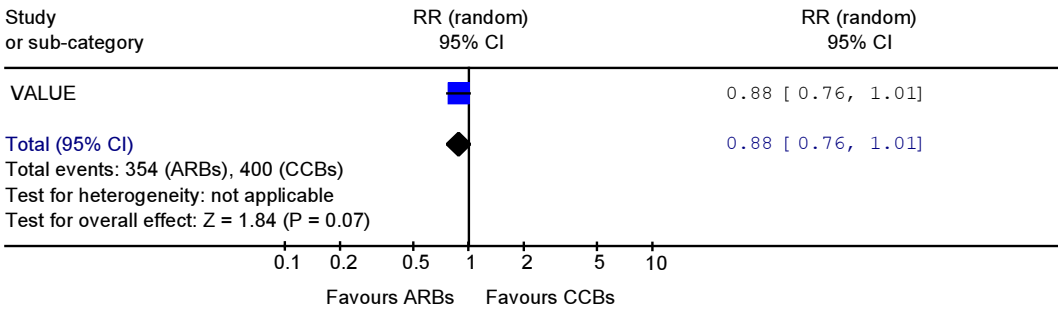
Comparison: **07 ARBs versus calcium-channel blockers**
Outcome: **02 Myocardial infarction**



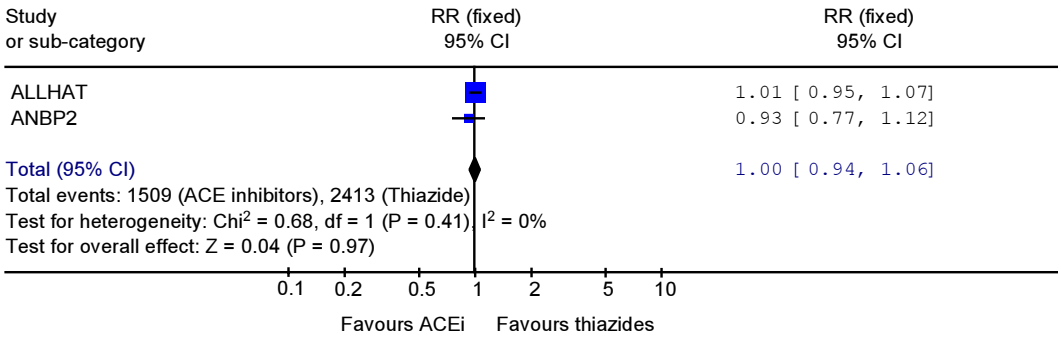
Comparison: 02 ARBs versus calcium-channel blockers
Outcome: 02 Stroke



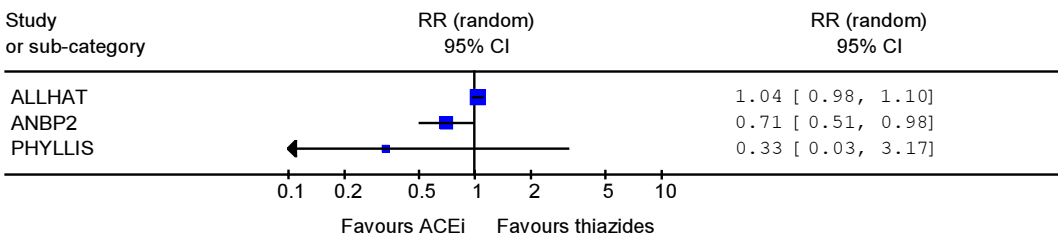
Comparison: 07 ARBs versus calcium-channel blockers
Outcome: 04 Heart failure



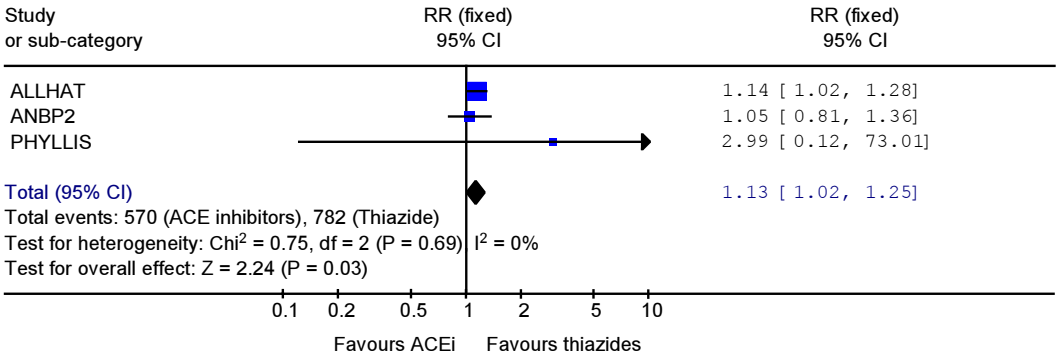
Comparison: 05 ACE inhibitors versus thiazides
Outcome: 01 Mortality



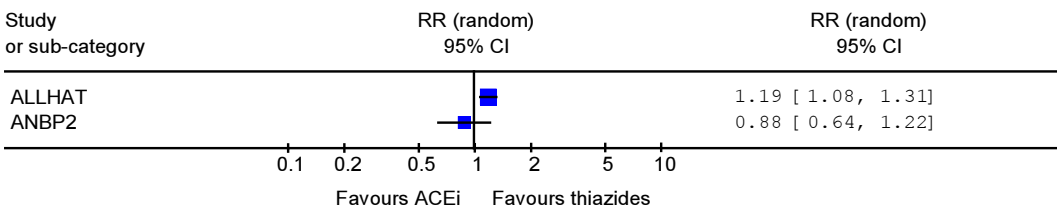
Comparison: 05 ACE inhibitors versus thiazides
Outcome: 02 Myocardial infarction



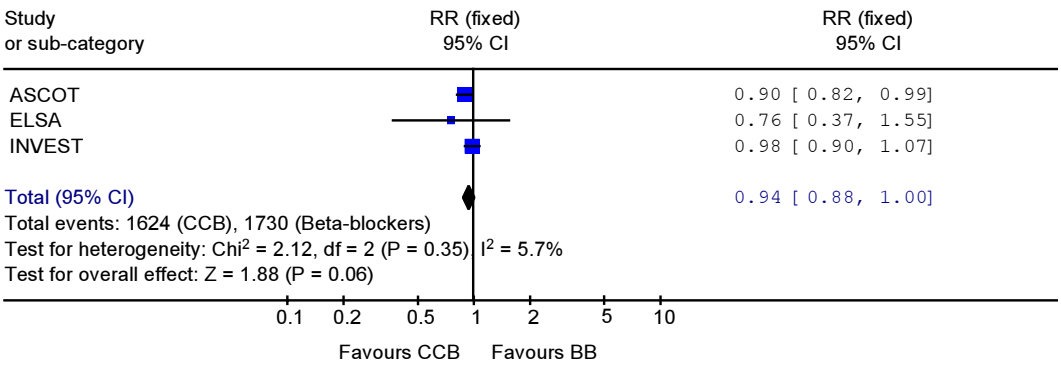
Comparison: **05 ACE inhibitors versus thiazides**
Outcome: **03 Stroke**



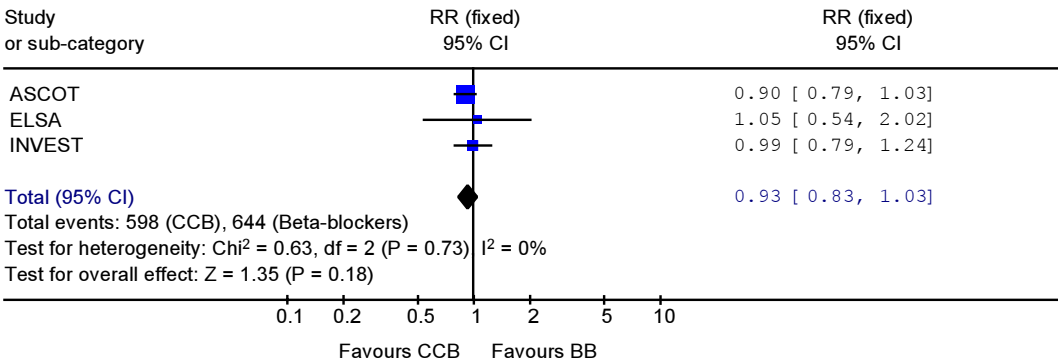
Comparison: **05 ACE inhibitors versus thiazides**
Outcome: **05 Heart failure**



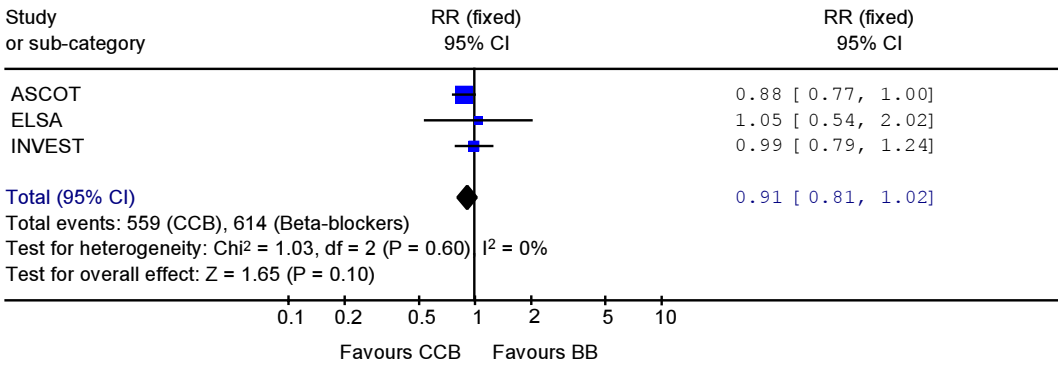
Comparison: **06 Calcium-channel blockers versus beta-blockers**
Outcome: **01 Mortality**



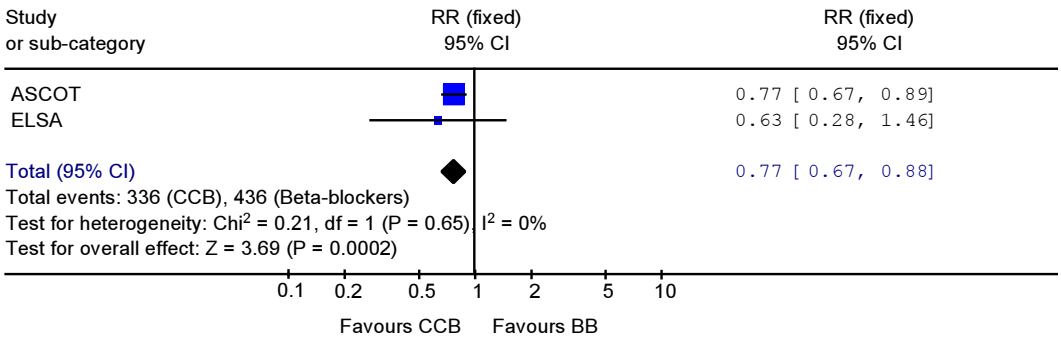
Comparison: **06 Calcium-channel blockers versus beta-blockers**
Outcome: **02 Myocardial infarction (including silent MI)**



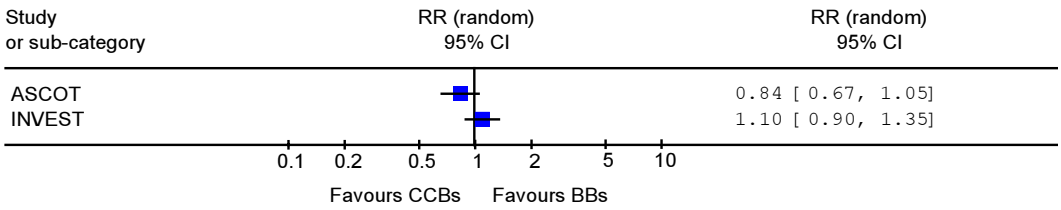
Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 03 Myocardial infarction (excluding silent MI)



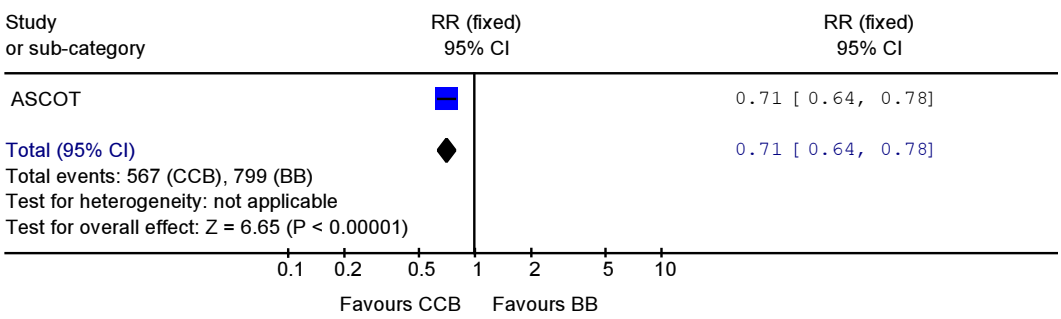
Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 04 Stroke

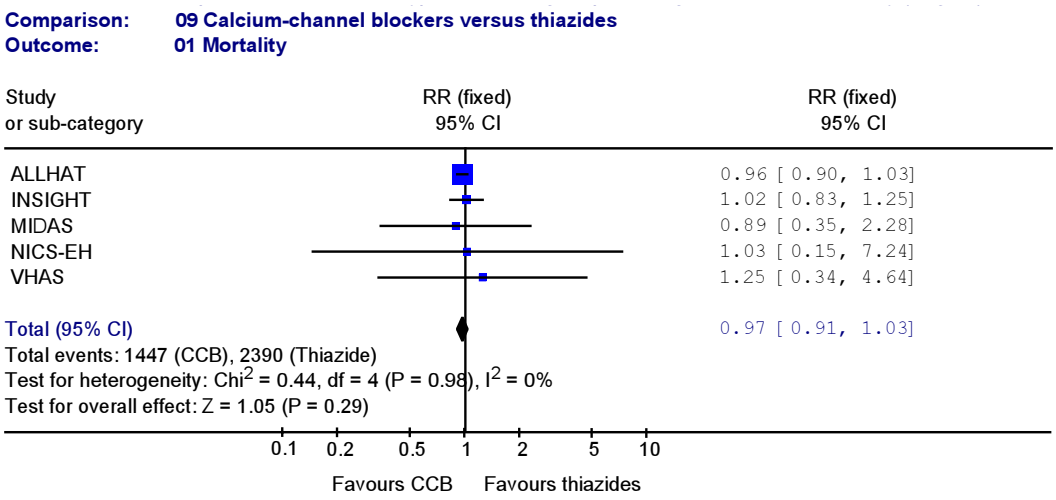


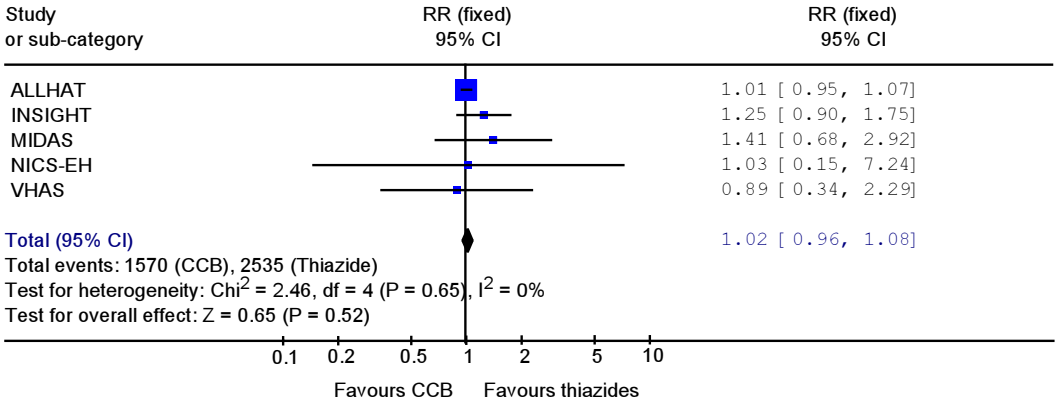
Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 06 Heart failure

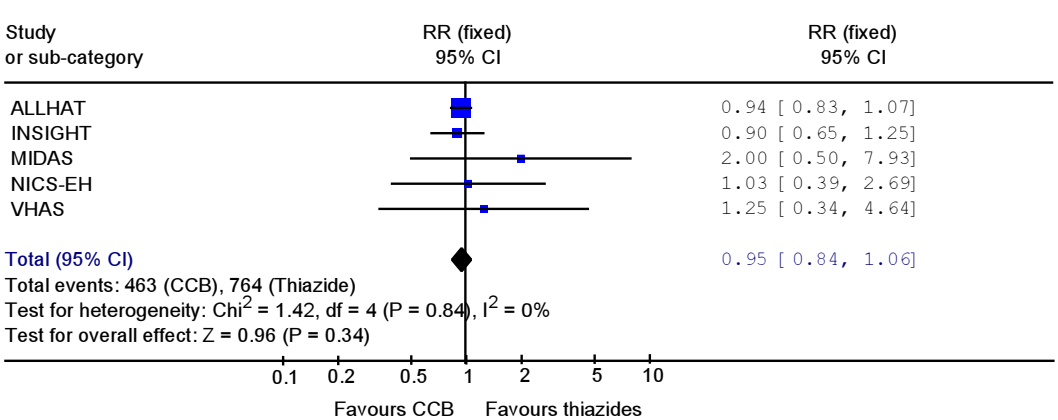


Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 06 Diabetes

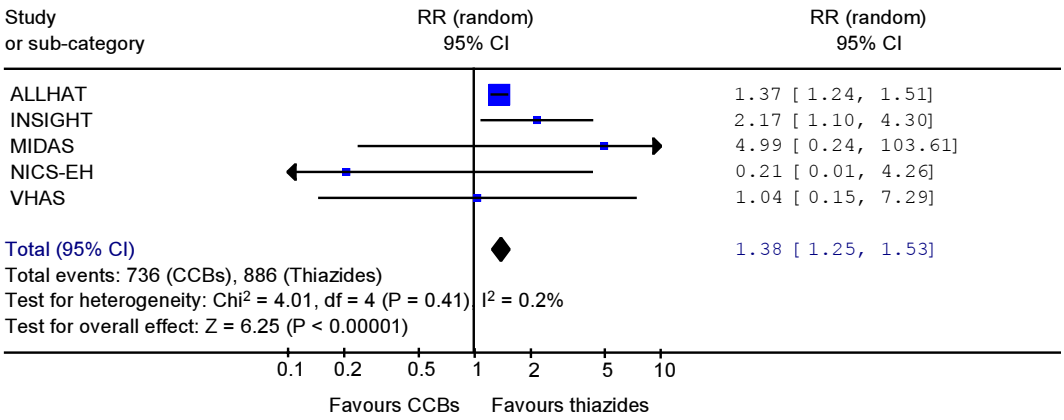



Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 01 Mortality
Study or sub-category
RR (fixed) 95% CI
RR (fixed) 95% CI
ALLHAT 0.96 [0.90, 1.03]
INSIGHT 1.02 [0.83, 1.25]
MIDAS 0.89 [0.35, 2.28]
NICS-EH 1.03 [0.15, 7.24]
VHAS 1.25 [0.34, 4.64]
Total (95% CI) 0.97 [0.91, 1.03]
Total events: 1447 (CCB), 2390 (Thiazide)
Test for heterogeneity: Chi2 = 0.44, df = 4 (P = 0.98), I2 = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
0.1 0.2 0.5 1 2 5 10
Favours CCB
Favours thiazides

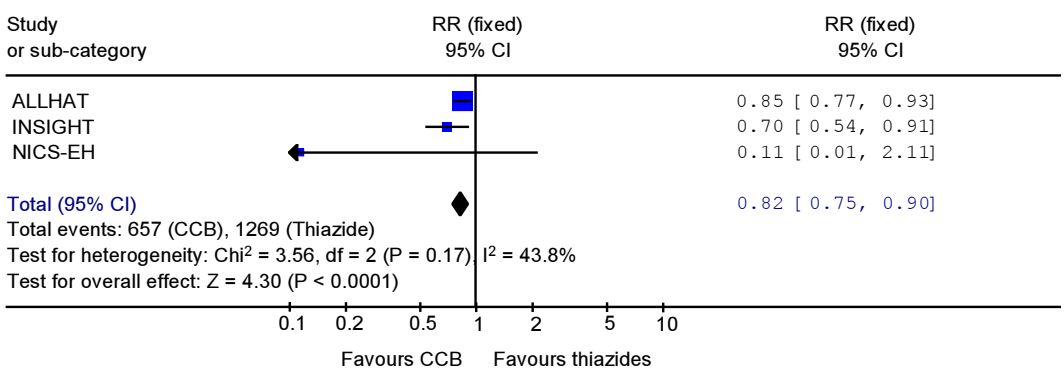

Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 02 Myocardial infarction
Study or sub-category
RR (fixed) 95% CI
RR (fixed) 95% CI
ALLHAT 1.01 [0.95, 1.07]
INSIGHT 1.25 [0.90, 1.75]
MIDAS 1.41 [0.68, 2.92]
NICS-EH 1.03 [0.15, 7.24]
VHAS 0.89 [0.34, 2.29]
Total (95% CI) 1.02 [0.96, 1.08]
Total events: 1570 (CCB), 2535 (Thiazide)
Test for heterogeneity: Chi2 = 2.46, df = 4 (P = 0.65), I2 = 0%
Test for overall effect: Z = 0.65 (P = 0.52)
0.1 0.2 0.5 1 2 5 10
Favours CCB
Favours thiazides


Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 03 Stroke
Study or sub-category
RR (fixed) 95% CI
RR (fixed) 95% CI
ALLHAT 0.94 [0.83, 1.07]
INSIGHT 0.90 [0.65, 1.25]
MIDAS 2.00 [0.50, 7.93]
NICS-EH 1.03 [0.39, 2.69]
VHAS 1.25 [0.34, 4.64]
Total (95% CI) 0.95 [0.84, 1.06]
Total events: 463 (CCB), 764 (Thiazide)
Test for heterogeneity: Chi2 = 1.42, df = 4 (P = 0.84), I2 = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
0.1 0.2 0.5 1 2 5 10
Favours CCB
Favours thiazides

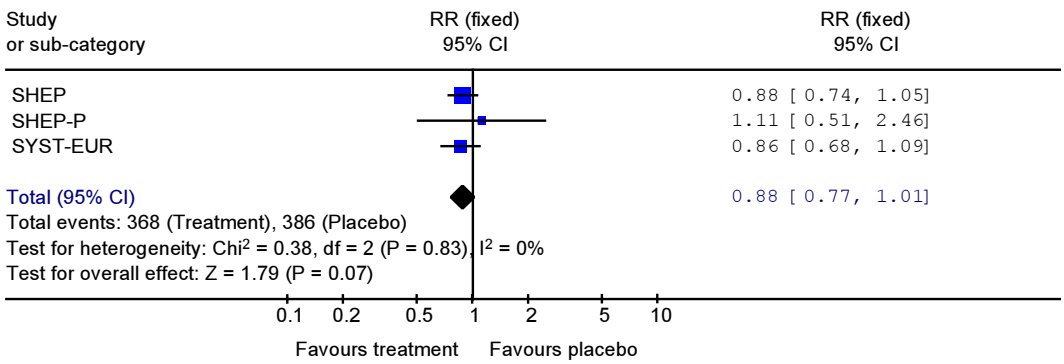
Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 05 Heart failure



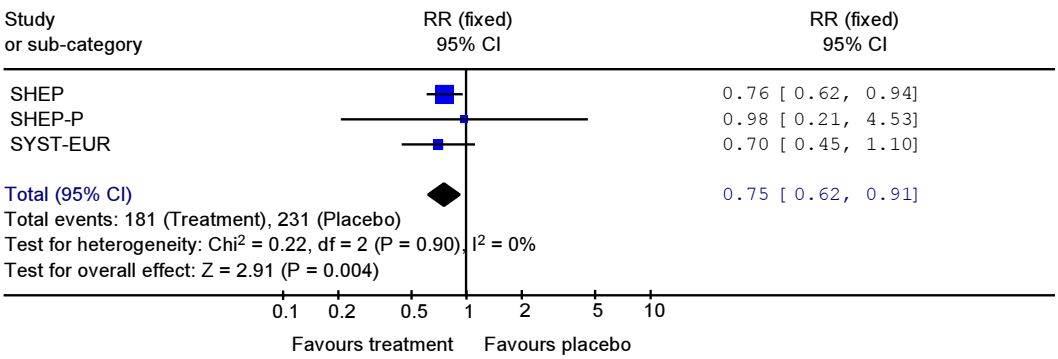
Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 05 Diabetes



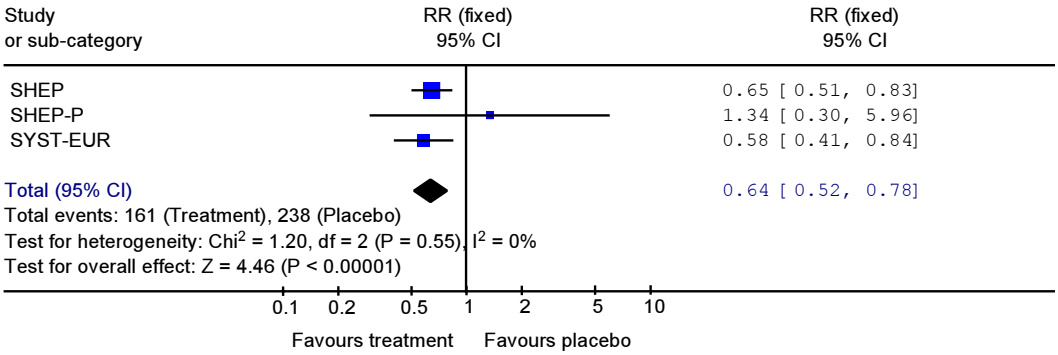
Comparison: 01 Antihypertensive drug therapy versus placebo
Outcome: 01 Mortality



Comparison: **01 Antihypertensive drug therapy versus placebo**
Outcome: **02 Myocardial infarction**



Comparison: **01 Antihypertensive drug therapy versus placebo**
Outcome: **03 Stroke**



Appendix B: Evidence tables – randomised controlled trials of pharmacological interventions

(The studies shaded in darker grey were found by the update literature search and are not included in the full NICE guideline *Hypertension (persistently high blood pressure) in adults*, 2004.)

The following abbreviations were used: ACEi = ACE inhibitors; ARB = angiotensin-II receptor antagonists; BB = beta-blockers; CABG = coronary artery bypass graft; CCB = calcium-channel blockers; CHD = cardiovascular heart disease; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DBP = diastolic blood pressure; GITS = gastrointestinal therapeutic system; ISH = isolated systolic hypertension; LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction; NR = not reported; SBP = systolic blood pressure.

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 anti-hypertensive 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) 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)	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. 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 25–100 mg/day, reserpine 0.05–0.2 mg/day or	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 v I3); p=0.30 (I2 v I3) I1: 481/3213 I2: 520/3210 I3: 821/53692.p=0.95 (I1 v I3); p=0.24 (I2 v I3) I1: 243/3213 I2: 260/3210 I3: 400/53693. p=0.49 (I1 v I3); p<0.001 (I2 v I3) I1: 145/3213	1. I1: 446/3213 I2: 678/3210 I3: 784/5369 2. I1: 115/3210 I2: 112/3213 I3: 186/5369 3. NR 4. At 4 years: I1: 60%

	clonidine 0.2–0.6 mg/day added Step 3: Hydralazine 50–200 mg/day					I2: 212/3210 I3: 257/53694. p=0.24 (I1 v I3); p<0.001 (I2 v I3) I1: 767/3213 I2: 836/3210 I3: 1211/5369	I2: 54% I3: 63%
2.	SBP/DBP <140/90					5. At 4 years: I1: 137/78 I2: 138/79 I3: 135/78	
ANBP2	I1: ACEi enalapril I2: diuretic hydrochlorothiazide Step 2: BB, CCB and ARBs added. 2. SBP <160 (or, if drug tolerated, <140) and reduction ? 20 DBP <90 (or, if drug tolerated <80) and reduction ?10	Australia. Adults (65–84) with previously treated (62%) and untreated (38%) hypertension (SBP >160 or BP >140/90). Exclusion criteria recent CVD events <6 months, life threatening illness or malignant hypertension	1. participant – no provider – no assessor – yes 2. adequate 3. adequate 4. 6,083 5. 4.1 years	1. yes 2. 72.0 3. 49.0% 4. 95%	1. 167.5/91.0 I1: 167.0/91.0 I2: 168.0/91.0 2. 13.0% 3. 7.5%	1. I1: 195/3,044 (6.4%) I2: 210/3,037 (6.9%) 2. I1: 58/3,044 (1.9%) I2: 82/3,037 (2.7%) 3. I1: 112/3,044 (3.7%) I2: 107/3,0397(3.5%) 4. I1: 394/3,044 (12.9%) I2: 429/3,037 (14.1%) 5. I1: 141(SD)/79(SD), 1,183 –26(SD)/–12(SD) I2: 142(SD)/79(SD), 1,183 –26(SD)/–12(SD)	1. I1: 1,278/3,044 (42.0%) I2: 1,155/3,039 (38.0%) 2. I1: 0/3,044 (0%) I2: 2/3,039 (0.1%) 3. I1: 65% I2: 67% 4. NR
ASCOT	I1: CCB amlodipine <10 mg/day, with ACEi perindopril as required I2: BB atenolol <100 mg/day, with bendroflumethiazide and potassium as required Step 2: alpha-blocker doxazosin GITS <8mg/day. With diabetes: SBP/DBP <130/80 Without diabetes: SBP/DBP <140/90	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, microalbuminuria/ proteinuria, elevated cholesterol or familial CHD)	1. open end-point 2. adequate 3. NR 4. 19,257 randomised 4. NR 5. 5.5 years (median)	1. good 2. 63.0 years 3. 77% 4. 95%	1. I1: 164/95 I2: 164/95 2. I1: LVH: 22% I2: LVH: 22% 3. I1: 2567/9639 (27%) I2: 2578/9618 (27%) 4. I1: 567/7072 I2: 799/7040 (6% v 8%)	1. I1: 738/9639 I2: 820/9618 2. Inc. silent MI I1: 429/9639 I2: 474/9618 Excluding silent MI 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	1. (Serious adverse events) I1: 162/9639 I2: 254/9618 2. I1: 121/9639 I2: 171/9618 3. I1: 15% I2: 9% 4. NR

continued

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
CAPPP	I1: ACEI captopril 50–100 mg/day I2: Diuretic hydrochlorothiazide 25 mg/day or bendroflumethiazide 2.5 mg/day and/or BB atenolol or metropolol 50–100 mg/day In I1, step 2 captopril 200mg/day, step 3 diuretic added and step 4 CCB added In I2, step 2 optimum dose of BB and diuretic and step 3 CCB added 2. DBP ?90	Sweden and Finland. Adults (25–66) with treated or untreated essential hypertension (DBP >100). Exclusion criteria renal disorders	1. participant – no provider – no assessor – yes 2. unclear 3. unclear 4. 10,985 5. 6.1 years	1. no – BP higher in captopril group 2. 52.6 3. 53.5% 4. NR	1. 160.7/98.9 I1: 161.8/99.8 I2: 159.6/98.1 2. 4–7% 3. 5.2%	1. I1: 184/5,478 (3.4%) I2: 190/5,480 (3.5%) 2. I1: 162/5,478 (2.9%) I2: 161/5,480 (2.9%) 3. I1: 189/5,478 (3.5%) I2: 148/5,480 (2.7%) 4. (deaths only) I1: I2: 5. (at 5 years) I1: 150.0(SD)/90.0(SD) –10.7(SD)/–8.9(SD), n/a I2: 149.0(SD)/89.0 –10.6(SD)/–9.1(SD), n/a	1. I: NR I2: NR 2. I: 14/5,492 (0.25%) I2: 13/5,493 (0.24%) 3. NR 4. NR
CONVINCE	I1: CCB verapamil 180–360 mg/day I2: BB atenolol 50–100 mg/day or diuretic hydro-chlorothiazide 12.5–25 mg/day (choice of drug determined by investigator) Step 2: hydrochlorothiazide 12.5–50 mg/day to verapamil or atenolol; or 50–100 mg/day atenolol to hydrochlorothiazide and step 3 other anti-hypertensive added 2. SBP<140 and/or DBP <90	North America, Europe, Middle East, Central America, South America. Adults (≥55) with currently treated hypertension (BP <175/100), untreated or treated <2 months hypertension (SBP 140–190 and DBP 90–110), and at least one other CVD risk (cigarette smoking, previous CVD, type II diabetes, obese)	1. participant – yes provider – no assessor – yes 2. adequate 3. unclear 4. 16,602 5. 2.2 years (median for blinded treatment) 6. 3 years (median)	1. yes 2. 65.6* 3. 44.0%* 4. 84.0%* * excluding 126 randomised participants because of data integrity concerns	1. 150.1/86.8 I1: 150.1/86.8 I2: 150.1/86.8 2. 12.3% 3. 19.7% (type II)	1. I1: 337/7,671 (4.4%) I2: 319/7,798 (4.1%) 2. I1: 133/7,671 (1.7%) I2: 166/7,798 (2.1%) 3. I1: 133/7,671 (1.7%) I2: 118/7,798 (1.5%) 4. I1: 262/7,671 (3.4%) I2: 243/7,798 /7,799 (3.1%) 5. I1: 136.5(SD)/79.0(SD), n/a –13.6(SD)/–7.8(SD) I2: 136.6(SD)/79.7(SD), n/a –13.5(SD)/–7.1(SD)	1. I1: 3,485/8,241 (42.3%) 3,086 stopped medication 62 excluded I2: 3,547/8,361 (42.4%) 3,164 stopped medication 64 excluded 2. I1: 570/8,241 (6.9%) I2: 563/8,361 (6.7%) 3. I1: 2,340/8,241 (28.4%) I2: 2,182/8,361 (26.1%) 4. I1: 65.5% I2: 65.9%

ELSA	1. I1: BB atenolol 50–100 mg/d I2: Calcium antagonist lacidipine 4–6 mg/d Step 2: diuretic hydrochlorothiazide 12.5–25 mg Nonrandomized cardiovascular treatment (antihypertensive or lipid-lowering agents) was given for 'variable time' to limited participants 2. DBP<95 mmHg and >5 mmHg reduction	France, Germany, Greece, Italy, Spain, Sweden, UK. Adults (45–75) with previously treated and treatment naive hypertension SBP 150–210 and DBP 95–115 mmHg. Exclude participants with no baseline or <1 follow up ultrasound carotid scan	1. subject – adequate provider – adequate assessor – unclear 2. adequate 3. unclear 4. 2,334 5. 3.8 years	1. yes 2. 56.0 3. 54.8% 4. 98.2%	1. 163.5/101.4 I1: 163.1/101.3 I2: 163.9/101.4 2: NR 3: NR	1. I1: 17/1,114 (1.5%) I2: 13/1,128 (1.2%) 2. I1: 17/1,114 (1.5%) I2: 18/1,128 (1.2%) 3. I1: 14/1,114 (1.2%) I2: 9/1,128 (0.8%) 4. I1: 73/1,114 I2: 69/1,128 5. I1: 141.5(SD)/85.7(SD) n –21.6(SD)/–15.6(SD) I2: 142.1(SD)/85.9(SD) n –21.8(SD)/–15.5(SD)	
HAPPHY	I1: Bendrofluazide 5 mg/day or hydrochlorothiazide 50 mg/day I2: Atenolol 100 mg/day or metoprolol 200 mg/day Step 2: hydralazine 75–150 mg/day added, step 3 spironolactone 75–150 mg/day added and step 4 other anti-hypertensive added 2. DBP <95	Western Europe, Czechoslovakia, USA. Men (40–64) with untreated or currently treated (35%) mild to moderate essential hypertension (DBP 100–130). Exclusion criteria history of MI, angina, CVA or other serious disease	1. participant – no provider – no assessor – yes 2. unclear 3. unclear 4. 6,569 5. 45.1 months	1. yes 2. 52.2 3. 100% 4. >99%	1. 166/107 I1: 166/107 I2: 166/107 2. 0% 3. 0%	1. I1: 101/3,240 (3.1%) I2: 96/3,265 (2.9%) 2. I1: 116/3,240 (3.6%) I2: 132/3,265 (4.0%) 3. I1: 41/3,240 (1.3%) I2: 32/3,265 (1.0%) 4. I1: 157/3,240 (4.8%) I2: 164/3,265 (5.0%) 5. I1: 140(SD)/89(SD), 3,204 –26(SD)/–18(SD) I2: 140(SD)/88(SD), 3,218 –26(SD)/–19(SD)	1. I1: 389/3,272 (11.9%) I2: 351/3,297 (10.6%) 2. I1: 32/3,272 (1.0%) I2: 32/3,297 (1.0%) 3. I1: 61.9% I2: 68.0% 4. BP did not differ between 2 groups

continued

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
INSIGHT	I1: CCB nifedipine 30–60 mg/day I2: Co-amilozide (diuretics hydrochlorothiazide 25–50 mg/day and amiloride 2.5–5 mg/day) Step 2: BB atenolol 25–50 mg/day or ACEI enalapril 25–50 mg/day added; step 3 other antihypertensive (not CCB or diuretic) added 2. <140/90 and reduction ?20/10	Western Europe and Israel. Adults (55–80) with essential hypertension (BP ≥150/95, or SBP ≥160) and at least one cardiovascular risk factor	1. participant – yes provider – yes assessors – yes 2. unclear 3. unclear 4. 6,575 5. 3.5 years	1. yes 2. 65 3. 46.4% 4. NR	1. 173/99 I1: 173/99 I2: 173/99 2. unclear 3. 20.6%	1. I1: 176/3,223 I2: 172/3,203 2. I1: 77/3,223 (2.4%) I2: 61/3,203 (1.9%) 3. I1: 67/3,223 (2.1%) I2: 74/3,203 (2.3%) 4. unclear 5. I1: 139.9(SD)/81.0(SD), 831 –33.1(SD)/–18.0(SD) I2: 139.0(SD)/82.5(SD), 944 –34.0(SD)/–16.5(SD)	1. I1: 1,430/3,289 (43.5%) I2: 1,189/3,286 (36.2%) 2. I1: 198/3,289 (6.0%) I2: 205/3,286 (6.2%) 3. I1: 61% I2: 58% 4. NR
INSIGHT – ISH substudy	1. I1: CCB nifedipine GITS 30mg/day with further titration as required. I2: Diuretics: hydrochlorothiazide 25 mg/day with amiloride 2.5 mg/day with further titration as required. Step 2: atenolol 25mg/day or enalapril 5mg/day 2. NR	Patients enrolled in INSIGHT study with ISH (SBP>140, DBP<90)	1. double-blind 2. NR 3. NR 4. 1,498 with ISH 5. NR 6. NR	1. good 2. NR 3. NR 4. NR	1. 173/88 2. NR 3. NR	1. I1: 38/738 I2: 48/760 2. NR 3. NR 4. NR 5. I1: 144/78 I2: 143/79	1. NR 2. NR 3. NR 4. NR
INVEST	1. I1: Verapamil sustained release, CCB 240 mg/day (+ trandolapril (ACE) 2 mg/d for patients	International. Adults (50 years >) with coronary artery disease and treated essential hypertension. Excluded if treated with BB within 2 weeks randomisation or in previous	1. subject – no provider – no assessor – yes 2. adequate) 3. adequate 4. 22,576	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%)	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%)

	with diabetes, renal impairment or heart failure) I2: Atenolol, BB 50 mg/day (+ trandolapril (ACE) 2 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 130/85 mmHg if diabetes or renal impairment	12 months for MI	5. 2.7 years			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	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%)
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

continued

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
LIFE	I1: ARB losartan 50 mg/day I2: BB atenolol 50 mg/day Step 2 hydrochlorothiazide 12.5 mg/day added, step 3 doubled dose of treatment drug, step 4 doubled dose of hydrochlorothiazide or other antihypertensive added 2. <140/90	Denmark, Finland, Iceland, Norway, Sweden, UK and USA. Adults (55–80) with hypertension (BP 160–200/95–115) and ECG signs of LVH. Exclusion criteria MI or CVA <6 months	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 9,222 5. 4.8 years	1. yes 2. 66.9 3. 45.9% 4. 92.2%	1. 174.4/97.8 I1: 174.3/97.9 I2: 174.5/97.7 2: 23.8% 3: 13.0%	1. I1: 383/4,557(8.4%) I2: 431/4,546(9.5%) 2. I1: 198/4,557(4.3%) I2: 188/4,546(4.1%) 3. I1: 232/4,557(5.1%) I2: 309/4,546(6.8%) 4. I1: 508/4,557(11.1%) I2: 588/4,546(12.9%) 5. I1: 144.1(17.1)/81.3(9.6), n/a –30.2(18.5)/–16.6(10.1) I2: 145.4(16.4)/80.9(9.6), n/a –29.1(19.2)/–16.8(10.1)	1. I1: 1,545/4,605(33.6%) I2: 1,780/4,588(38.8%) 2. I1: 48/4,605 (1%) I2: 42/4,588 (0.9%) 3. I1: 11% I2: 11% 4. I1: 48% I2: 45%
LIFE – Black substudy	1. I1: ARB losartan 50mg/day I2: BB atenolol 50mg/day Step 2: hydrochlorothiazide 12.5mg/day Step 3: double treatment drugs Step 4: double step 2 drugs or other antihypertensive drug 2. SBP/DBP <140/90	Worldwide black patients enrolled in the LIFE study	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 533 black patients 5. 4.7 years (all patients)	1. NR 2. NR 3. NR 4. 0%	1. (black US patients) I1: 172/98 I2: 172/98 2. NR 3. 13%	1. NR 2. p=0.141 I1: 13/270 (4.8%) I2: 6/263 (2.3%) 3. p=0.030 I1: 24/270 (8.9%) I2: 12/263 (4.6%) 4. NR 5. I1: 142/81 I2: 143/81	1. NR 2. NR 3. NR 4. NR

LIFE – ISH+LVH substudy	1. I1: ARB losartan 50mg/day I2: BB atenolol 50mg/day Step 2: hydrochlorothiazide 12.5mg/day Step 3: double treatment drugs Step 4: double step 2 drugs or other antihypertensive drug 2. SBP/DBP <140/90	Worldwide patients with ISH (SBP>160, DBP<90) and LVH enrolled in the LIFE trial	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 1326 ISH+LVH patients 5. 4.7 years (all patients)	1. good 2. 70 years 3. 40% (approx) 4. 92% (approx)	1. I1: 174/83 I2: 175/82 2. I1: 24% I2: 21% 3. I1: 16% I2: 20%	1. p=0.03 I1: 66/660 (10%) I2: 93/666 (14%) 2. p=0.54 I1: 31/660 (4.7%) I2: 36/666 (5.4%) 3. p=0.020 I1: 32/660 (4.8%) I2: 56/666 (8.4%) 4. NR 5. p=0.67/0.04 I1: 146/75 I2: 146/74	1. NR 2. NR 3. NR 4. I1: 44% I2: 43%
MIDAS	I1: CCB isradipine 2.5–5 mg/day I2: Diuretic hydrochlorothiazide 25–50 mg/day Step 2: ACEi enalapril 2.5–10 mg/day added. 2. DBP <95 and reduction ?10	USA. Adults (≥40) with essential hypertension (DBP 90–115) and confirmed carotid atherosclerosis. Exclusion criteria recent history of CVA, MI, renal disease, or type I diabetes	1. participant – yes provider – yes assessors – yes 2. unclear 3. unclear 4. 883 5. 36 months	1. yes 2. 58.4 3. 78% 4. 72%	1. 149.7/96.5 I1: 150.6/96.7 I2: 148.9/96.2 2. 1.9% 3. 0	1. I1: 8/442 (1.8%) I2: 9/441 (2.0%) 2. I1: 17/442 (1.4%) I2: 12/441 (2.0%) 3. I1: 6/442 (1.4%) I2: 3/441 (0.7%) 4. (includes angina, CHF, sudden death) I1: 25/442 (5.7%) I2: 14/441 (3.2%) 5. (SBP at 3 years, DBP at 6 months) I1: 133.4(18.1)/83.7(SD), n/a –17.2(SD)/–13.0(SD) I2: 130.0(12.2)/83.2(SD), n/a –19.5(SD) /–13 (SD)	1. I1: 96/442 (21.7%) 9.3% adverse reaction I2: 90/441 (20.4%) 8.2% adverse reaction 2. NR 3. I1: 55.5% I2: 54.2% 4. NR

continued

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
MRC	I1: Bendroflumethiazide 10 mg/day I2: BB propranolol 240 mg/day C: Placebo Step 2: methyldopa added to I1 and methyldopa or guanethidine added to I2; no stepped care in C 2. DBP <90 within 6 months	UK. Adults (35–64) with untreated essential hypertension (SBP <200 and DBP 90–109). Exclusion criteria MI/CVA <3 months, angina or diabetes	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 17,354 5. 4.9 years	1. yes 2. 52.0 3. 52.1% 4. unclear	1. 161.4/98.2 I1: 161.4/98.5 I2: 161.4/98.5 C: 161.3/98.0 2. NR 3. 0%	1. I1: 128/3,519 (3.6%) I2: 120/3,558 (3.4%) C: 253/6,941 (3.6%) 2. I1: 119/3,519(3.4%) I2: 103/3,558(2.9%) C: 234/6941(3.4%) 3. I1: 18/3,519 (0.5%) I2: 42/3,558 (1.2%) C: 109/6,941 (1.6%) 4. I1: 140/3,519 (4.0%) I2: 146/3,558 (4.1%) C: 352/6,941 (5.1%) 5. I1: 135.8(SD)/84.8(SD), n/a –25.6(SD)/–13.7(SD) I2: 139.2(SD)/85.8(SD), n/a –22.2(SD)/–12.7(SD) C: 148.7(SD)/90.8(SD), n/a –12.6(SD)/–7.2(SD)	1. I1: 1,770/4,297 (41.2%) I2: 1,925/4,403 (43.7%) C: 4,031/8,654 (46.6%) 2. I1: 778/4,297 (18.1%) I2: 845/4,403 (19.2%) C: 1,713/8,654 (19.8%) 3. I1: 70.8% I2: 77.9% C: NR 4. I1: 75% I2: 73% C: 46%
MRC-O	I1: BB atenolol 50–100 mg/day I2: Diuretic hydrochlorothiazide 25–50mg/day plus diuretic amiloride 2.5–5 mg/day C: Placebo Step 2: other trial drug added; step 3 nifedipine 20 mg/day and/or other supplementary drugs added in I; no stepped	UK. Adults (65–74) with currently untreated essential hypertension (SBP 160–209). Exclusion criteria MI/CVA <3 months, impaired renal function or diabetes	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 4,396 5. 5.8 years	1. yes 2. 70.3 3. 41.8% 4. unclear	1. 184.7/90.6 I1: 184.7/90.8 I2: 184.8/91.0 C: 184.7/90.4 2. unclear 3. 0%	1. I1: 167/1,102 (15.2%) I2: 134/1,081 (12.4%) C: 315/2,213 (14.2%) 2. I1: 80/1,102 (7.3%) I2: 48/1,081 (4.4%) C: 159/2,213 (7.2%) 3. I1: 56/1,102 (5.1%) I2: 45/1,081 (4..2%) C: 134/2,213 (6.1%) 4. I1: 151/1,102(13.7%)	1. I1: 861/1,102 (78.2%) I2: 653/1,081 (60.4%) C: 1,488/2,213 (67.2%) 2. I1: 349/1,102 (31.7%) I2: 358/1,081 (33.1%) C: 916/2,213 (41.4%) 3. I1: 48% I2: 62% C: NR 4. NR

	care in C 2. ? 150 if baseline SBP <180 and SBP ? 160 if baseline SBP ? 180					I2: 107/1,081 (9.9%) C: 309/2,213 (14.0%) 5. unclear	
NICS-EH	I1: CCB nicardipine hydrochloride 40–80 mg/day I2: Diuretic trichlormethiazide 2–4 mg/day 2. Not reported	Japan. Adults (≥60) with currently treated (61%) or untreated (39%) essential hypertension (SBP 160–220 and DBP <115). Exclusion criteria CVD	1. participant – yes provider – yes assessor – unclear 2. unclear 3. adequate 4. 429 5. 4.6 years	1. no (greater % women in I1) 2. 69.8 3. 33.1% 4. 0%	1. 172.3/93.8 I1: 171.9/94.2 I2: 172.6/93.4 2. 0 3. 0	1. I1: 2/204 (1%) I2: 2/210 (1%) 2. I1: 2/204 (1%) I2: 2/210 (1%) 3. I1: 8/204 (4%) I2: 8/210 (4%) 4. I1: 10/204 (5%) I2: 10/210 (5%) 5. I1: 147.0(15)/81.0(8), 106 –24.9(SD)/–13.2(SD) I2: 147.0(16)/79.0(9), 94 –25.6(SD)/–14.4(SD)	1. I1: 57/215 (26.5%) 2.8% adverse reactions 3.7% BP too high 6.0% took other antihypertension agents I2: 65/214 (30.4%) 4.2% adverse reactions 7.5% BP too high 5.6% took other antihypertension agents 2. I1: 11/215 (5.1%) I2: 4/214 (1.9%) 3. not applicable 4. not applicable
PHYLLIS	1. I1. Hydrochlorothiazide 25 mg qid and pravastatin in 50% of patients I2. ACEi fosinopril 20mg qid and pravastatin in 50% of patients Step 2: nifedipine GITS 30–60 mg/day. 2. DBP <90 or <95 with a fall of at least 10 mmHg	Patients in Italy age >45, <70 with hypertension, hypercholestoremia, asymptomatic carotid atherosclerosis and no previous cardiovascular event	1. double blind 2. adequate 3. NR 4. 508 randomised 4. NR 5. 2.6 years	1. I2 fewer smokers 2. 58 years 3. 40% 4. NR	1. 160/98 (approx) 2. NR 3. NR	1. NR 2. I1: 3/253 I2: 1/254 3. I1: 0/253 I2: 1/254 4. I1: 0/253 I2: 1/254 5. NR	1. NR 2. NR 3. I1: 82% (approx) I2: 82% (approx) 4. NR

continued

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
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; matching stepped care in C 2. SBP <160 baseline SBP ? 180 and reduction >20 if baseline SBP 160–179	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 5. 4.5 years	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% 3. 10.1%	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. 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)	1. I: 448/1221 (36.7%) 3% received known active therapy as BP was too high 13% stopped 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%
SHEP-P	I: Chlorthalidone 25–50 mg/day C: Placebo Step 2: one of the following drugs assigned at random, reserpine 0.1–0.2 mg/day, metoprolol 100–200 mg/day, hydralazine 50–100 mg/day in I; matching stepped care in C 2. SBP <160 or ? 20 below baseline	USA. Adults (≥60) with systolic hypertension (SBP 160–219, DBP <90), 47% previously treated. Exclusion criteria MI <6 months, coronary bypass surgery <2 years, uncontrolled congestive heart failure or insulin	1. participant – yes provider – yes assessor – yes 2. inadequate 3. adequate 4. 551 5. 34 months	1. yes 2. 72 3. 36.8% 4. 81.6%	1. 172.4/75.4 I: 172/75 C: 174/77 2. 5% 3. excluding insulin-dependent diabetes	1. I: 32/443 (7.2%) C: 7/108 (6.5%) 2. I: 8/443(1.8%) C: 2/108(1.9%) 3. I: 11/443 (2.5%) C 6/108 (5.6%) 4. unclear 5. I: 142(40)/68(8), 224 –30(SD)/–7(SD) C: 159(40)/73(8), 61 –15(SD)/–4(SD)	1. I: 115/315 (37%) C: 36/80 (45%) 2. I: 0/443 (0%) C: 0/108 (0%) 3. I: 87% C: 43% 4. After one year: I: 80% C: 40%

STOP-H2	I1: ACEi enalapril or lisinopril 10 mg/day I2: CCB felodipine or isradipine 2.5 mg/day I3: BB atenolol 50 mg/day, metoprolol 100 mg/day, pindolol 5 mg/day or diuretics hydrochlorothiazide 25 mg/day and amiloride 2.5 mg/day Step 2: if started on ACEi or BB, hydrochlorothiazide and amiloride 25/2.5 mg/day added. If started on CCB or diuretic, atenolol 50mg/day, metoprolol 100mg/day, or pindolol 5mg/day added 2. ? 160/95	Sweden. Adults (70–84) with treated or untreated essential hypertension (BP ≥180–230/90–120, and/or DBP >105). Exclusion criteria MI or CVA ≤12 months	1. participant – no provider – no assessor – yes 2. unclear 3. adequate 4. 6,614 5. 60 months	1. yes 2. 76.0 3. 33.2% 4. unclear	1. 194/98 I1: 194/98 I2: 194/98 I3: 194/98 2. 8–15% 3. 10.9%	1. I1: 380/2,205 (17.2%) I2: 362/2,196 (16.5%) I3: 369/2,213 (16.7%) 2. I1: 139/2,205 (6.3%) I2: 179/2,196 (8.2%) I3: 154/2,213 (7.0%) 3. I1: 215/2,205 (9.8%) I2: 207/2,196 (9.4%) I3: 237/2,213 (10.7%) 4. I1: 437/2,205 (41.9%) I2: 450/2,196 (43.6%) I3: 460/2,213 (44.1%) 5. (at 54 months) I1: 159(SD)/81(SD), n/a –35(SD)/–17(SD) I2: 159(SD)/80(SD), n/a –35(SD)/–18(SD) I3: 158(SD)/81(SD), n/a –36(SD)/–17(SD)	1. I1: 853/2,205 (38.7%) I2: 742/2,196 (33.8%) I3: 834/2,213 (37.7%) 2. I1: 0/2,205 (0%) I2: 0/2,196 (0%) I3: 0/2,213 (0%) 3. NR 4. NR
SYST-EUR	I: Nitrendipine 10–40 mg/day C: Placebo Step 2: enalapril 5–20 mg/day added and step 3 hydrochlorothiazide 12.5–25 mg/day added in I; matching stepped care in C 2. SBP <150 and reduction ≤20	Europe. Adults (≥60) with previously treated or untreated isolated systolic hypertension (sitting SBP 160–219 and DBP <95 and standing SBP ≥140). Exclusion criteria renal disease, congestive heart failure, dissecting aortic aneurysm, CVA or MI <1 year or any severe concomitant disease	1. participant – yes provider – yes assessors – yes 2. adequate 3. unclear 4. 4,695 5. median 2 years	1. yes 2. 70.2 3. 33.1% 4. NR	1. 173.8/85.5 I: 173.8/85.5 C: 173.9/85.5 2. 29.9% 3. 10.5%	1. I: 123/2,277 (5.4%) C: 137/2,181 (6.3%) 2. I: 33/2,277 (1.4%) C: 45/2,181 (2.1%) 3. I: 47/2,277 (2.1%) C: 77/2,181 (3.5%) 4. Incl. heart failure I: 186/2,277 (8.2%) C: 137/2,181 (6.3%) 5. I: 152.5(SD)/77.5(SD), 705 –21.3(17.6)/–2.0(9.0) C: 163.2(SD)/85(SD), 682 –10.6(17.6)/–1.5(9.0)	1. I: 626/2,398 (26.1%) C: 766/2,297 (33.3%) 2. I: 121/2,398 (5.0%) C: 116/2,297 (5.1%) 3. I: 216/601 (36%) C: 95/574 (17%) 4. at median 2 years: I: 43.5% C: 21.4%

continued

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
VALUE	I1. ARB (valsartan): <160mg/day I2. CCB (amlodipine): <10mg/day Step 2: hydrochlorothiazide <25 mg/day as required. Step 3: other antihypertensive drug as required SBP/DBP <140/90	Patients without recent MI, CABG, CVA older than 50 years with hypertension and at least one CV risk factor (male, LVH, elevated cholesterol, diabetes or renal impairment)	1. double blind 2. block randomisation 3. NR 4. 15,313 randomised 5. 3.6 years 6. 4.2 years	1. good 2. 67 years 3. 58% 4. 89%	1. I1: 155/87 I2: 155/88 2. I1: 46% I2: 46% (CAD) 3. NR 4. I1: 690/7649 I2: 845/7596 (13% v 16%)	1. I1: 841/7649 I2: 818/7596 2. I1: 369/7649 I2: 313/7596 3. I1: 322/7649 I2: 281/7596 4. I1: 810/7649 I2: 789/7596 5. I1: 139/79 I2: 138/78	1. (adverse events) I1: 11.9% I2: 12.9% 2. I1: 120/7649 I2: 131/7596 3. NR (fewer in I1) 4. I1: 56% I2: 62%
VHAS	I1: CCB verapamil 240 mg/day I2: Diuretic chlorthalidone 25 mg/day Step 2: ACEi captopril 25–50 mg/day added 2. DBP ≥90 or ≥95 and >10% reduction	Italy. Adults (40–65) with essential hypertension (BP ≥160/95). Exclusion criteria CVA, MI <6 months, renal failure, type I diabetes mellitus or uncontrolled type II diabetes mellitus	1. participant – yes provider – yes (Note double blind design for first 6 months only, then open design) assessor – yes 2. unclear 3. unclear 4. 1,414 5. 2 years	1. yes 2. 54.2 3. 48.9% 4. unclear	1. 169.0/102.3 I1: 169.1/102.2 I2: 168.8/102.3 2. 5.0 3. 3.6%	1. I1: 5/707 (0.7%) I2: 4/707 (0.6%) 2. I1: 8/707 (1.1%) I2: 9/707 (1.3%) 3. I1: 5/707 (0.7%) I2: 4/707 (0.6%) 4. unclear 5. I1: 140.2(SD)/85.7(SD), 166 –28.6(SD)/–16.6(SD) I2: 141.5(SD)/85.2(SD), 158 –27.6(SD)/–17(SD)	1. I1: 158/707 (23.5%) 2.5% adverse events I2: 166/707 (22.3%) 2.5% adverse events 2. I1: 0/707 (0%) I2: 0/707 (0%) 3. I1: 44.1% I2: 38.8% 4. I1: 69.3% I2: 66.9%

Appendix C: Hypertension guideline – results of the economic analysis

Economic question

The aim of the model was to estimate the cost effectiveness of the various blood pressure lowering drug classes for the management of hypertension in primary care.

Population and subgroups

The model considered patients with essential hypertension seen in primary care, excluding those with pre-existing CVD, heart failure (HF) or diabetes. It was designed to be run separately for different cohorts, defined by age (55, 65, 75 and 85) and sex. In addition, the model classified these cohorts by baseline CVD risk (0.5%–5% per year), by heart failure risk (0–5% per year) and by diabetes risk (0–5% per year).

The base case analysis presented below shows the results for 65-year-old men and women with 2% CVD risk, 1% HF risk and 1.1% diabetes risk. Sensitivity analysis are also presented showing whether and how the results vary by age, sex, CVD, HF and diabetes risk.

The model is based on trial evidence that included relatively few younger (under 55) or black patients, so the results may not be reliable for these groups. However, speculative sensitivity analyses were conducted to explore how different assumptions about treatment effects might impact on the cost-effectiveness results for younger (under 45) and black patients (people from Black African and Black Caribbean ethnic groups).

Interventions compared

The analysis assessed the costs and effects of alternative drugs alongside a 'do nothing' comparator. Inclusion of no treatment as an option is important for economic evaluations as it allows identification of low-risk groups for whom treatment is not likely to be cost effective.

The interventions compared were thus:

- no intervention (NI)
- thiazide-type diuretics (D)
- calcium-channel blockers (C)
- beta-blockers (B)
- ACE inhibitors/angiotensin-II receptor antagonists (A).

It was assumed that 80% of patients will be on ACE inhibitors and 20% will be on ARBs, because of an inability to tolerate ACE inhibitors (expert opinion). The costs and effects of the drugs were weighted to take account of this.

For simplicity, only first-line drugs were considered. However, it should be noted that the relative treatment effects from the meta-analysis include additional benefits from various second- and third-line treatments offered in the trials.

Outcomes

The treatment effects were measured in terms of prevention of CVD events: non-fatal unstable angina, MI, heart failure and stroke, and CVD-related deaths. Other CVD events, including onset of stable angina, peripheral vascular disease and transcient ischaemic attacks were not modelled, because data on them are not consistently reported in the trials.

The only side effects modelled were onset of HF and diabetes. Other side effects were not modelled in the base case analysis, although the possible impact of adverse reactions to the drugs in sensitivity analyses was examined. It should also be noted that the model does not explicitly include cost impacts of withdrawals, non-concordance or transfers between treatments. The impact of such changes on effectiveness is implicitly included through the use of intention-to-treat trial data.

Health outcomes for the cost-effectiveness analysis are summarised in the form of quality-adjusted life-years (QALYs), where one QALY represents one year of healthy life.

Model structure and assumptions

A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with alternative drugs for the management of hypertension in primary care from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people move between the states. Figure C1 shows a schematic representation of the patients' pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, unstable angina, stroke, diabetes, heart failure or death) while the remainder stay in the event-free state. Patients can experience more than one non-fatal event in subsequent periods of the model. Ultimately, all patients end up in the death state.

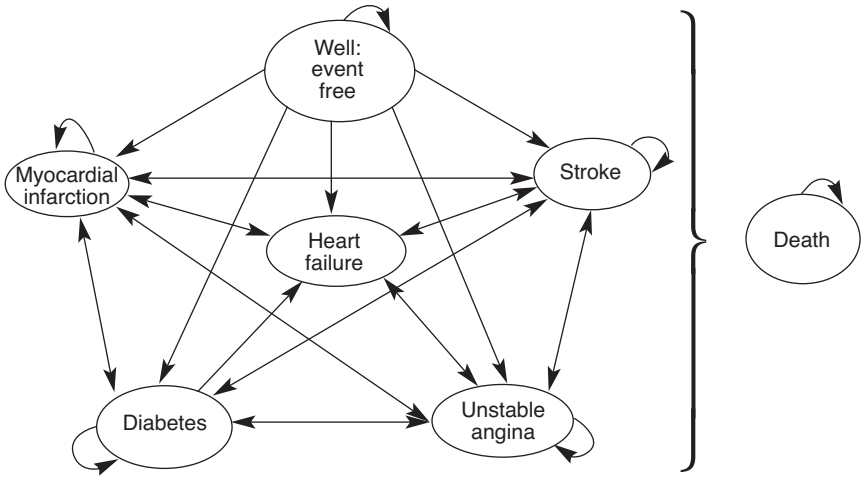


Figure C1 Model structure for hypertension

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (6 months). These transition probabilities are adjusted for each subgroup by age, sex, ethnicity, baseline CVD, HF risk and diabetes risk. For illustration, the equivalent annual transition probabilities for untreated 65-year-old men and women with 2% CVD, 1% HF risk and 1.1% diabetes risk are shown in Tables C1 and C2. Unless better data for a hypertensive population were available, the probabilities are based on those used in a recent analysis of the cost effectiveness of statins developed by the University of Sheffield's School of Health and Related Research (ScHARR) for the NICE appraisal.[62] The GDG advised on this and other data used in the model.

The model is run first assuming that the cohort was to receive no intervention (NI). The model is then re-run for each active treatment (A, B, C and D) with transition probabilities adjusted to reflect the expected reduction in CVD events and diabetes and HF incidence from the clinical meta-analysis. Healthcare costs and QALYs are then estimated for each option (NI, A, B, C and D) by weighting the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is lifetime, with an assumed upper age of 100, by which time most of the cohort have died. Because of the nature of Markov models, some proportion of the cohort remain alive, no matter how high the mortality rates are assumed to be. In the base case model 98% of the 65-year-old cohort died by the age of 100.

Table C1 Probabilities for a 65-year-old untreated man with 2% annual CVD risk

Parameter	Annual probability (%)	Source
Well to unstable angina	0.0017	Statins model
Well to MI	0.0035	Statins model
Well to diabetes	0.0110	ASCOT trial
Well to stroke	0.0054	Statins model
Well to HF	0.0098	SHEP
Well to death	0.0180	Statins model and population life tables
Unstable angina to MI	0.0300	Statins model
Unstable angina to diabetes	0.0067	Assumed to be the same as MI to diabetes
Unstable angina to stroke	0.0095	Assumed to be the same as MI to stroke
Unstable angina to HF	0.0230	Assumed to be the same as MI to HF
Unstable angina to death	0.0348	Statins model and population life tables
MI to unstable angina	0.0078	HOPE
MI to MI	0.0721	Statins model
MI to diabetes	0.0067	HOPE

continued

Table C1 Probabilities for a 65-year-old untreated man with 2% annual CVD risk – *continued*

Parameter	Annual probability (%)	Source
MI to stroke	0.0095	Statins model
MI to HF	0.0230	HOPE
MI to death	0.0258	Statins model and population life tables
Diabetes to unstable angina	0.0033	Double the risk of the well population
Diabetes to MI	0.0069	Double the risk of the well population
Diabetes to stroke	0.0108	Double the risk of the well population
Diabetes to HF	0.0197	Double the risk of the well population
Diabetes to death	0.0359	Double the risk of the well population
Stroke to unstable angina	0.0016	Assumed to be the same as stroke to MI
Stroke to MI	0.0016	Statins model
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model
Stroke to HF	0.0115	Assumed to be half of MI to HF
Stroke to death	0.3548	Statins model and population life tables
HF to unstable angina	0.0230	Assumed to be the same as HF to MI
HF to MI	0.0230	SOLVD
HF to stroke	0.0103	SOLVD
HF to HF	0.0545	SOLVD
HF to death	0.0768	SOLVD and population life tables

Table C2 Probabilities for a 65-year-old untreated woman with 2% annual CVD risk

Parameter	Annual probability (%)	Source
Well to unstable angina	0.0010	Statins model
Well to MI	0.0024	Statins model
Well to diabetes	0.0110	ASCOT trial
Well to stroke	0.0076	Statins model
Well to HF	0.0098	SHEP
Well to death	0.0141	Statins model and population life tables

continued

Table C2 Probabilities for a 65-year-old untreated woman with 2% annual CVD risk – *continued*

Unstable angina to MI	0.0300	Statins model
Unstable angina to diabetes	0.0067	Assumed to be the same as MI to diabetes
Unstable angina to stroke	0.0095	Assumed to be the same as MI to stroke
Unstable angina to HF	0.0230	Assumed to be the same as MI to HF
Unstable angina to death	0.0307	Statins model and population life tables
MI to unstable angina	0.0078	HOPE
MI to MI	0.0721	Statins model
MI to diabetes	0.0067	HOPE
MI to stroke	0.0095	Statins model
MI to HF	0.0230	HOPE
MI to death	0.0217	Statins model and population life tables
Diabetes to unstable angina	0.0021	Double the risk of the well population
Diabetes to MI	0.0048	Double the risk of the well population
Diabetes to stroke	0.0153	Double the risk of the well population
Diabetes to HF	0.0196	Double risk of well
Diabetes to death	0.0283	Double the risk of the well population
Stroke to unstable angina	0.0016	Assumed to be the same as stroke to MI
Stroke to MI	0.0016	Statins model
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model
Stroke to HF	0.0115	Assumed to be half of HF to MI
Stroke to death	0.3507	Statins model and population life tables
HF to unstable angina	0.023	Same as MI to HF
HF to MI	0.023	SOLVD
HF to stroke	0.0103	SOLVD
HF to HF	0.0545	SOLVD
HF to death	0.0727	SOLVD and population life tables

Baseline risks

The probabilities of primary CVD events by age for a 45-year-old cohort with initial CVD risk of 2% are shown in Table C3. CVD risk was assumed to rise at the rate of 0.03% per annum for men and 0.008% per annum for women (estimated from the Health Survey for England data 1998 by ScHARR). The proportion of first CVD events that were unstable angina, MI, stroke or death were taken from the age-specific UK incidence rates used in the ScHARR statins model. In the statins model they obtained their data from the Bromley Coronary Heart Disease Register and Oxfordshire Community Stroke Project. The risk of new-onset diabetes in the baseline model (1.1%) was taken from the metabolically neutral arm of the ASCOT trial. The incidence of heart failure in the baseline model (0.98%) was taken from the placebo arm of the SHEP trial.

The risk of CVD-related mortality was estimated from CVD incidence in the cohort, and the proportion of CVD events estimated to be fatal (from the ScHARR model). Non-CVD related mortality by age and sex (Table C4) was taken from the life tables for England and Wales prepared by the Government Actuaries Department (GAD) and from data on the proportion of deaths due to CVD-related causes from the Office for National Statistics. In the base-case model it was assumed that the hypertensive cohort was not at increased risk of non-CVD death compared with the general population. However, this assumption was tested in the sensitivity analysis, raising the cohort's relative risk from 1 to 8.

The risk of secondary or subsequent events, following unstable angina, MI, stroke or HF are shown in Table C5. The increased risks of mortality and other CVD events for patients who develop diabetes were assumed to be twice those seen in non-diabetic patients. The British Hypertension Society guideline (2004)[63] noted that the increase in CVD risk in men is twice, while in women it is four-fold. This assumption was tested in sensitivity analysis. Probabilities of having unstable angina, HF and diabetes after an MI were taken from HOPE, which was a secondary prevention trial. The probability of having diabetes after a stroke was assumed to be the same as that of having diabetes from MI. The probabilities of unstable angina (UA), MI, stroke, HF and CVD death following onset of heart failure were taken from the placebo arm of the SOLVD trial. Because of a lack of data, it was also assumed that transitions from UA to diabetes, HF and stroke and from stroke to unstable angina were the same as those seen in the MI population (expert opinion). It was also assumed that the risk of HF following a stroke is half that following MI.

Table C3 Baseline incidences of primary events in untreated population

Distribution of primary cardiovascular disease events

			Men		
Age	**UA %**	**MI %**	**Stroke %**	**CVD death %**	**Other* %**
45	10.7	29.5	12.9	10.1	36.8
55	7.1	17.2	20.6	13.4	41.7
65	8.3	17.3	27.0	16.0	31.4
75	8.1	16.1	34.3	14.3	27.2
85	9.6	18.6	35.1	13.7	23.0

Source: ScHARR statins model. (**www.nice.org.uk/pdf/statins_assessment_report.pdf**)

			Women		
Age	**UA %**	**MI %**	**Stroke %**	**CVD death %**	**Other* %**
45	11.7	8.0	22.9	9.1	48.3
55	7.3	9.2	28.8	10.6	44.1
65	5.2	12.1	38.2	17.1	27.4
75	3.4	10.2	46.4	15.2	24.8
85	2.9	10.0	50.1	14.7	22.3

Annual probability of primary cardiovascular disease events

			Men		
Age	**UA %**	**MI %**	**Stroke %**	**CVD death %**	**Total risk %**
45	0.21	0.59	0.26	0.20	2.00
55	0.16	0.40	0.47	0.31	2.30
65	0.22	0.45	0.70	0.42	2.60
75	0.23	0.47	0.99	0.41	2.90
85	0.31	0.60	1.12	0.44	3.20

			Women		
Age	**UA %**	**MI %**	**Stroke %**	**CVD death %**	**Total risk %**
45	0.23	0.16	0.46	0.18	2.00
55	0.15	0.19	0.60	0.22	2.08
65	0.11	0.26	0.83	0.37	2.16
75	0.08	0.23	1.04	0.34	2.24
85	0.07	0.23	1.16	0.34	2.32

*Stable angina and TIA. UA = unstable angina; MI = myocardial infarction

Table C4 Baseline non-cardiovascular disease related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales

	All cause ICD10: A00–R99		Circulatory ICD: I00–I99		Non-circulatory as proportion of all deaths	
	Men	Women	Men	Women	Men %	Women %
45	12,417	8,139	3,930	1,362	0.68	0.83
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58

Source: Office for National Statistics (**www.statistics.gov.uk/STATBASE/Expodata/Spreadsheets/D8986.xls**)

All cause mortality, estimated from life tables, 2002–04, England and Wales

	Annual probability of death in age band	
	Men %	Women %
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

Source: Government Actuary's Department (**www.gad.gov.uk/Life_Tables/Interim_life_tables.htm**)

Estimated non-circulatory deaths for hypertensive cohort

	Annual probability of death in age band	
	Men %	Women %
45	0.25%	0.20%
55	0.61%	0.47%
65	1.48%	1.07%
75	3.18%	2.41%
85	5.17%	4.65%

Table C5 Baseline incidences of secondary events in untreated population

After	Transition to	Annual risk	Source
Unstable angina (UA)	UA	No recurrence	Expert opinion
	MI	0.03000	Statins model
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.00950	Assumed same as MI to stroke
	HF	0.02300	Assumed same as MI to HF
	CVD death	0.02000	Statins model
MI	UA	0.00775	HOPE
	MI	0.07210	Statins model
	Diabetes	0.00667	HOPE
	Stroke	0.00950	Statins model
	HF	0.02300	HOPE
	CVD death	0.01100	Statins model
Stroke	UA	0.00160	Assumed same as for stroke to MI
	MI	0.00160	Statins model
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.28750	Statins model
	HF	0.01150	Assumed half rate for MI to HF
	CVD death	0.34000	Statins model
HF	UA	0.02300	SOLVD
	MI	0.02300	SOLVD
	Stroke	0.01025	SOLVD
	HF	0.05450	SOLVD
	CVD death	0.06200	SOLVD

Treatment effects

The relative treatment effects of these interventions were taken from the meta-analysis done for the guideline update. Comparisons including data from large recent studies were chosen to estimate the treatment effects for the economic evaluation: D versus NI, C versus D, C versus B and C versus A (Table C6). Sensitivity analyses were conducted for two other scenarios: firstly by replacing the estimate for B with a comparison with D (Table C7) and secondly by replacing the estimate for ACE inhibitors with a comparison with C (Table C8).

Table C6 Relative risks of drugs (base case analysis)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
Unstable angina	0.893	0.881	0.984	0.970
MI	0.780	0.796	0.855	0.816
Diabetes	0.985	0.808	1.137	0.720
Stroke	0.690	0.656	0.851	0.731
Heart failure	0.530	0.731	0.761	0.642
Death	0.910	0.883	0.939	0.902

Table C7 Relative risks of drugs (scenario 1: B versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
Unstable angina	0.893	0.881	0.984 *	0.970
MI	0.780	0.796	0.835	0.812**
Diabetes	0.985	0.808	1.138 *	0.720
Stroke	0.690	0.656	0.794	0.722**
Heart failure	0.530	0.731	0.762 *	0.642
Death	0.910	0.883	0.901	0.895**

* Based on B versus C comparison, since B versus D were not available for this outcome.
** These figures change because the effects of ARBs are based on a comparison with B.

Table C8 Relative risks of drugs (scenario 2: ACEi versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
Unstable angina	0.893	0.881	0.984	0.970 *
MI	0.780	0.796	0.855	0.816
Diabetes	0.985	0.808	1.138	0.720 *
Stroke	0.690	0.656	0.851	0.751
Heart failure	0.530	0.731	0.762	0.642
Death	0.910	0.883	0.939	0.895

* Based on ACEi versus C comparison since A versus D were not available for this outcome.

Cost data

The NICE reference case specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and/or metabolic disease. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. Costs are at 2005 prices. As per current NICE guidance, an annual discount rate of 3.5% was used for both costs and health benefits.

The costs of health states used in the model are shown in Table C9. Costs of stroke were taken from the Statins health technology assessment (HTA).[62] Costs of diabetes were based on estimates from a NICE submission done by ScHARR when they evaluated the use of sibutramine for the treatment of obesity.[64] Costs for revascularisation are included in the costs of MI and UA. Costs of acute MI (non-fatal reinfarction) were assumed to be the same as those of patients on thrombolysis, which includes the cost of hospitalisation.[65] Costs of unstable angina were assumed to the same as those of acute coronary syndrome and were taken from Palmer, 2004.[66] Heart failure costs were taken from the NHS reference cost 2005/06.

Drug costs were taken from the prices quoted in the Drug Tariff, based on the usual dose for hypertension. In the base case model we used the cost for the most commonly used drug in each class. The impact of using the cheapest and most expensive drug in each class was also tested in sensitivity analyses (Table C10).

Table C9 Costs of health states

Health state	£ Cost/year	Source
Unstable angina	2,107	Palmer 2004
Subsequent unstable angina costs	440	Statins model
MI	4,448	Hartwell 2005
Post-MI costs	500	NICE Hypertension guideline 2004
Diabetes	753	Ara 2004
Stroke	8,046	Statins model
Post-stroke costs	2,163	Statins model
Heart failure	2,350	NHS reference costs
Post-heart failure costs	500	Assumed to be same as post MI
Death	0	

Table C10 Drug costs

	Cost per year (£)		
	Drug used in the model	**Cheapest drug**	**Most expensive drug**
ACEi	Ramipril: £29.64	Enalapril: £19	Trandolapril: £ 152
ARB	Losartan: £217	Candesartan: £119	Losartan: £217
Beta blocker	Atenolol: £13	Atenolol: £13	Acebutolol: £243
CCB	Amlodipine: £70	Diltiazem: £39	Nicardipine: £218
DD	Bendroflumethiazide: £17	Bendroflumethiazide: £17	Xipamide: £51

Source: Prescription Pricing Authority, January 2006.

Quality of life (utility)

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the QALY approach. This requires estimates of survival and quality of life associated with each health state included in the model.

The utility values used in the model are shown in Tables C11 and C12. The Statins model did an extensive literature search to identify the best available utility estimates for the various health states. Thus estimates for MI, unstable angina, and stroke were taken from Statins HTA. Diabetes and heart failure estimates were taken from the Harvard Cost-Effectiveness Analysis (CEA) registry database (**www.hsph.harvard.edu/cearegistry/data/phaseIpreferenceweights.pdf**). For MI and UA a higher utility was applied after the initial six months. For diabetes, stroke and HF a constant utility from onset of the condition was assumed.

As in the Statins model, utilities were adjusted to reflect the fact that health-related quality of life in the general population decreases with age (ie multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996).

Antihypertensive medication may be expected to have two opposing effects on quality of life: improvements through the reduced incidence of CVD events (as discussed above) and reductions through the impact of treatment-related adverse effects. The latter could potentially be important in assessing the balance between benefits and harms, particularly for low-risk individuals. Differences in adverse effects between the drugs could also have an influence on their relative cost effectiveness. A Medline search was done to identify utility estimates that could be used to reflect the latter for the included drug classes. Some studies were identified that estimated the incidence of drug-related adverse events and quality of life.[67–74] However, none of these included data in a form suitable for estimation of utilities. Most published cost-effectiveness studies have assumed zero, or minimal (0.01), loss of quality of life due to treatment-related side effects (Harvard CEA Registry[75]). Where these have compared different antihypertensive medications, they have generally assumed equal utility loss from adverse effects of treatment.[76–77] Few studies have directly measured treatment utilities from patients. The economic analysis of the SCOPE trial included direct assessment of utility using the

EuroQoL health status measurement instrument.[78] This estimated a mean change in utility of minus 0.03 for the candesartan group and minus 0.05 for the mixed hypertensive treatment control group over a mean follow-up of 3.7 years. However, it is not possible to separate out the impact of treatment side effects, or to attribute utility losses to individual drugs. Another cost-effectiveness study[79] estimated utilities from 148 hypertensive patients using the standard gamble technique. They found a net loss in utility of 0.027, but did not report any difference by drug.

Given this paucity of information, we assumed no loss of utility due to adverse effects of the drugs in the base case model. However, we did a sensitivity analysis to investigate how large any such effects would have to be to change the results.

Table C11. Health state utility weights

Health state	Utility weight	Source
MI (first 6 months)	0.76	Statins
Post MI	0.88	Harvard CE Registry
Unstable angina (first 6 months)	0.77	Statins
Post UA	0.80	Assumption
Stroke	0.63	Statins
Diabetes	0.90	Harvard CE Registry
Heart failure	0.71	Harvard CE Registry
Death	0.00	Statins

Table C12. Utility weight by age

Age group	Age utility weight	Source
45–54	0.85	DH Health Survey for England 1996
55–64	0.79	DH Health Survey for England 1996
65–74	0.78	DH Health Survey for England 1996
75+	0.73	DH Health Survey for England 1996

DH = Department of Health.

Cost effectiveness

The results of cost-effectiveness analysis are usually presented as incremental cost-effectiveness ratios (ICERs), which determine the additional cost of using one drug (X) per additional QALY gained compared with no intervention or another drug (Y).

ICERs = (cost of X – cost of Y)/(QALY of X – QALY of Y)

Where more than two interventions are being compared, the ICERs are calculated using the following process:

1 The drugs are ranked in terms of cost (from the cheapest to the most expensive).
2 If a drug is more expensive and less effective than the previous one, then it is said to be 'dominated' and is excluded from further analysis.
3 ICERs are calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next more effective strategy, then it is ruled out by 'extended dominance'. This means that there is some mixture of two other strategies that is more effective and less expensive.
4 ICERs are recalculated excluding any drugs subject to extended dominance.[66]

Sensitivity analysis

The model includes a base case analysis supplemented with univariate deterministic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

Results

Base case results

The base case results are presented in Table C13 for 65-year-old men and women with an annual CVD risk of 2%, HF risk of 1% and diabetes risk of 1.1%. This suggests that antihypertensive treatment is cost effective for this population and that the most cost-effective initial drug in this group is calcium-channel blockers (C). The ICER of C compared with thiazide-type diuretics (D) is about £12,000 to £13,000 per QALY gained, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

Beta-blockers (B) are ruled out by simple dominance, since D is estimated to be cheaper and more effective. This is illustrated in Figure C2, since B lies to the northwest of D. The ACEi/ARB option (A) is also ruled out by extended dominance, since treating some patients with D and the remainder with C would be cheaper and more effective than A: in Figure C2, A lies to the northwest of a straight line joining points D and C. However, it should be noted that the absolute difference between A and C is small.

Table C13 Base case results (65 year old, 2% risk, 1.1% diabetes risk, 1% HF risk)

Men

	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,360	10.12	–
NI	£4,390	9.49	–
B	£4,530	9.80	–
A	£5,020	10.15	–
C	£5,110	10.19	£12,250

continued

Table C13 Base case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% HF risk) – *continued*

Women

	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,670	10.55	–
NI	£4,740	9.87	–
B	£4,870	10.20	–
A	£5,340	10.57	–
C	£5,430	10.61	£13,490

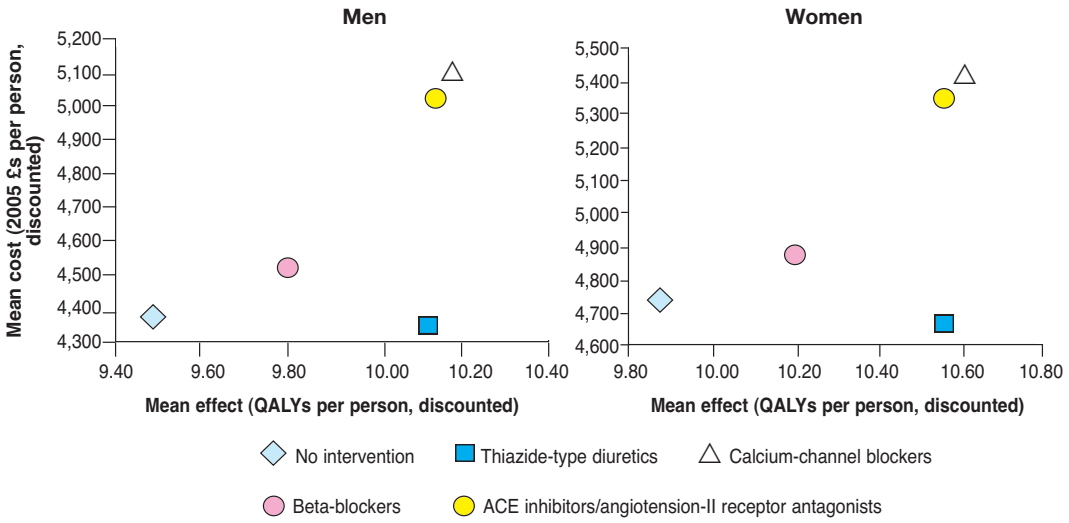


Figure C2 Base case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% HF risk)

Results for patient subgroups

Table C14 and Figures C3 and C4 show how cost effectiveness is estimated to vary with age, sex, CVD risk, diabetes risk and heart failure risk. The table shows the most cost-effective option for each subgroup, based on a conservative cost-effectiveness threshold of £20,000 per QALY. The meta-analysis found that thiazide-like diuretics and CCBs have similar effects on the incidence of MI, stroke and death. However, CCBs are associated with significantly higher rates of heart failure but lower rates of diabetes. Thus, CCBs appear to be a more cost-effective option for over-55s at relatively low risk of heart failure and for those at relatively high risk of diabetes.

ACE inhibitors or ARBs appear to be a cost effective alternative to CCBs at high levels of diabetes risk and intermediate levels of HF risk. This is because they are associated with lower rates of heart failure and diabetes, but higher rates of stroke.

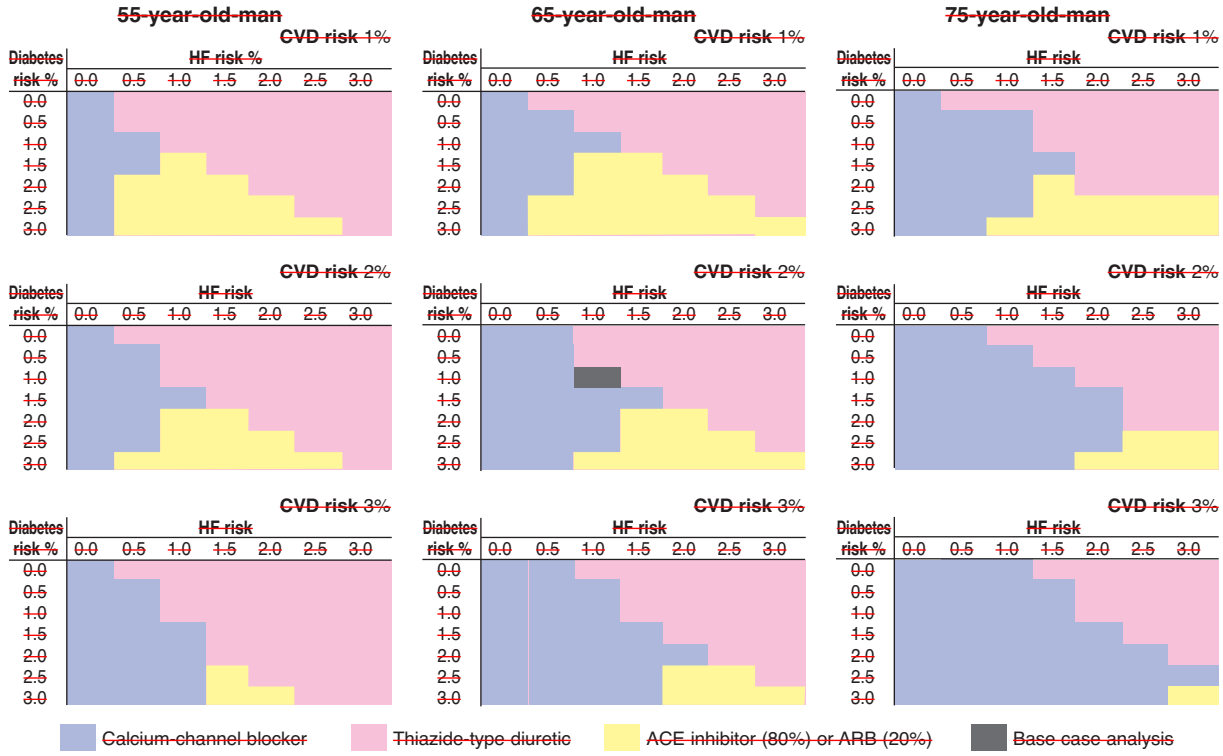


Figure C3 Most cost-effective first-line drug for men by age and annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year. HF = heart failure; ARB = angiotensin-II receptor antagonists.

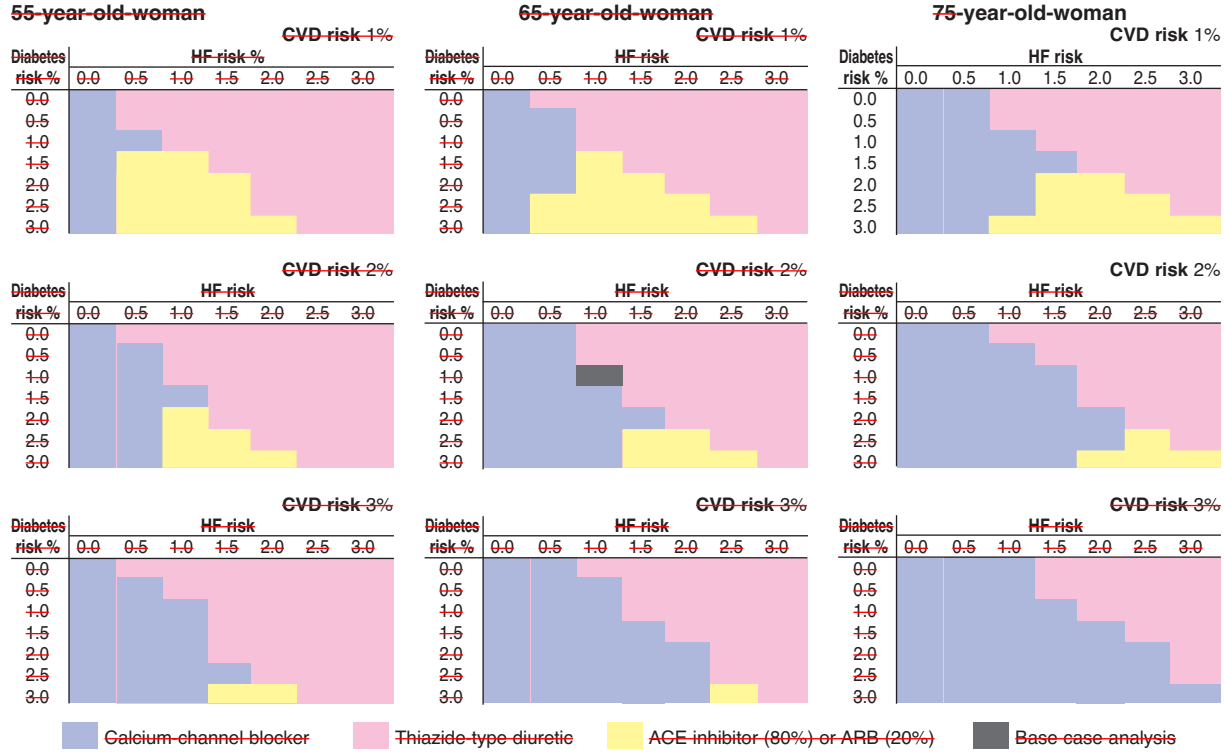


Figure C4 Most cost-effective first-line drug for women by age and annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year. HF = heart failure; ARB = angiotensin-II receptor antagonists.

Younger patients

The model is not designed to estimate cost effectiveness for a younger population, since most of the evidence about treatment effects derives from studies in older people. However, we can use the model to test the possible impact of improved performance of ACEi, ARBs and BBs in a younger, non-black group. Taking the predicted baseline effects of a 45-year-old cohort (at 2% annual CVD risk, 1% annual heart failure risk and 1.1% annual diabetes risk), cost effectiveness for given percentage improvements was estimated in treatment effects for ACEi/ARB and BB compared with the meta-analysis figures.

In the base case model, diuretics appear to be the most cost-effective option for this group. However, if the relative risks for ACEi/ARBs were only about 1.7% or better than the meta-analysis estimates, then they would be cost effective (cost per QALY less than £20,000). Beta-blockers continued to be dominated even at higher percentage improvements, assuming an equal percentage improvement of ACEi/ARBs and BBs for the younger population. This analysis does lend some support to the hypothesis that ACEi/ARBs may be cost effective in younger non-black patients.

Other sensitivity analyses

A range of univariate sensitivity analyses were conducted to assess the impact of different input parameters on the base case results. In these analyses we held all other parameters fixed at their base case values. The results are interpreted using a conservative cost-effectiveness threshold of £20,000 per QALY.

Detailed results for all parameters are shown in the appendix. Table C14 (overleaf) summarises the results for those parameters that led to a change of conclusion from the base case. These results are discussed further below.

Uncertainty over treatment effects

The results are sensitive to uncertainty over the magnitude of treatment effects estimated from the meta-analyses.

- Diuretics dominate all other options when the effects of CCBs compared with diuretics are increased to their upper 95% confidence limits.
- ACEi/ARB are the most cost-effective option in four tested scenarios:
  - Upper limits for effects of C versus B (£8,000 per QALY for A versus B).
  - Lower limits for effects of ACEi versus C (£3,000 per QALY for A versus D).
  - Lower limits for effects of ARB versus B (£5,400 per QALY for A versus D).
  - Lower limits for effects of ACEi versus D (£3,700 per QALY for A versus D).
- Beta-blockers are the most cost-effective option if we take the lower limits for the effects of B versus D (£1,200 per QALY for B versus D).

These extreme results may be relatively unlikely, however, since the relative risks for all outcomes would all have to be simultaneously at their lower 95% limits.

Table C14 Sensitivity analysis results that altered base case conclusions

Parameter	Most cost-effective option
Base case	C: £12,250 per QALY for men (C versus D)
Upper limits for effects of C versus D	D: D dominates other interventions
Upper limits for effects of C versus B	A: £8,000 per QALY (A versus B)
Lower limits for effects of ACEi versus C	A: £3,000 per QALY (A versus D)
Lower limits for effects of ARB versus B	A: £5,400 per QALY (A versus D)
Scenario 1: lower limits for effects of B versus D	B: £1,200 per QALY (B versus D)
Scenario 1: lower confidence limit for treatment effect of ARB versus B	A: £4,600 per QALY (A versus D)
Scenario 2: lower limits for effects of ACEi versus D	A: £3,700 per QALY (A versus D)
More than 63% of patients on ARBs	A: >£20,000 per QALY (A versus C)
Cost of CCBs more than £105 per annum	D: >£20,000 per QALY (C versus D/A)
RR of CVD with diabetes less than 1.3, compared with risks for 'well' cohort	D: >£20,000 per QALY (C versus D)
RR of CVD with HF more than 2.4, compared with risks with HF in base case model	D: >£20,000 per QALY (C versus D)
Reduction in quality of life from drug side effects 4% or more	NI: all active interventions dominated
Reduction in quality of life of 0.1% or more due to side effects of C	D: >£20,000 per QALY (A versus D)

Use of ARBs

The percentage of ARBs used in conjunction with ACEi in the base case model was assumed to be 20%. Assuming that 50% of patients were on ARBs and 50% on ACEi did not change the base case conclusions. However, as the use of ARBs approached 70% and beyond, the ACEi/ARB combination became cost effective. The use of ARBs alone (100%) resulted in an estimated ICER compared with CCBs of about £15,800 per QALY.

Cost of CCBs

In the base case model, CCBs were assumed to cost £70 per patient per annum (based on the drug tariff price of amlodipine, January 2006). If this is increased to £105 or more, then CCBs are no longer cost effective compared with diuretics.

Risk of CVD events for people with diabetes

The results are sensitive to the relative risk of CVD events for people with diabetes. For a given level of diabetes risk, the cost effectiveness of CCBs improves as the relative risk of CVD events

for people with diabetes increases. At an initial diabetes risk of 1.1% per annum, CCBs are no longer cost effective compared with diuretics if the relative risk of CVD events with diabetes is 1.3 or lower.

- Risk of CVD events for people with heart failure

The results are sensitive to the relative risk of CVD events for people with heart failure. For a given level of heart failure risk, the cost effectiveness of CCBs worsens as the relative risk of CVD events for people with heart failure increases. This may be explained by the fact that D does better in preventing heart failure than CCBs. At 1% annual risk of heart failure, CCBs are no longer cost effective compared with diuretics if the risks of CVD events with heart failure are more than 2.3 times higher than in the base case.

- Quality of life due to drug side effects

The base case model assumes there is no loss in quality of life due to hypertensive treatment side effects. If the loss of quality of life due to the side effects of hypertensive treatment is assumed to be 4% or greater, then treatment may not be cost effective. This assumes equal quality of life loss for all drugs, which is unlikely given that we know that there are differing rates of adverse events and withdrawals.

Small differences in adverse effects of the different drugs may change their relative cost effectiveness. Holding all other parameters constant at their base case values, CCBs remain the most cost effective option provided that their impact on quality of life due to adverse effects does not exceed about 0.1%. For comparison, the quality of life impact of chronic lower extremity oedema has been estimated at 10% (Harvard CEA registry). Thus, if an individual experiences even minor or infrequent side effects with CCBs, then alternative antihypertensive treatment may be more cost effective.

Limitations of the model

The model was based on various assumptions that could possibly bias the results.

Firstly, it assumed that treatment effects from the meta-analysis were attributable to the first-line drug. However, the percentage of patients remaining on monotherapy in the trials varied widely: from about 60% in ALLHAT to about 10% in ASCOT, for example. The above results will therefore tend to overestimate the effectiveness and cost effectiveness of hypertensive treatment compared with no intervention. However, this is unlikely to change the overall conclusions. If we assume that 90% of patients receive a second drug at the price of £60 per annum, the ICER for diuretics versus NI only increases to around £1,100 per QALY, and for CCBs versus diuretics increases to about £12,400 per QALY.

There might be a more serious problem if some trials used more or less effective protocols following failure to achieve blood pressure targets on the first drug, introducing bias to the estimates of relative effectiveness between the first-line drugs. This issue also applies to the interpretation of the clinical evidence from the meta-analysis of trials.

A second limitation of the model derives from the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends

only on their current health state (there is no longer 'memory' in the model). Thus the probability of new-onset diabetes for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and healthcare costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost effective than they may be in reality. So the model is conservative in this respect.

A third potentially important limitation of the model is the lack of utility data for the side effects of the different drugs. The relative ranking of CCBs, ACEi/ARBs and thiazide-like diuretics is quite sensitive to assumptions about their relative side effects. Further research in this area is likely to be worthwhile.

Fourth, the lack of data on relative treatment effects for under-45s and black people means that it is difficult to predict the relative cost effectiveness of the different drugs in these subgroups. Evidence exists on differences in blood pressure response by age and ethnicity. However, extrapolating this evidence to longer-term outcomes (CVD events and incidence of diabetes) is more difficult.

A fifth limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost effectiveness of treatment. On the other hand, concordance and continuation of treatment may well differ between the trial context and routine practice.

Because of the short timescales for the guideline update it has not been possible to conduct a probabilistic sensitivity analysis with the model. This further analysis would be useful, particularly given the sensitivity of the results to extreme assumptions about the relative treatment effects.

Conclusions

This analysis suggests that the cost effectiveness of drugs for first-line treatment of essential hypertension largely depends on their relative effects on the prevention of diabetes and heart failure. The model predicts that for people at low risk of heart failure, CCBs are the most cost-effective option because they are associated with a low risk of diabetes and they also have a good effectiveness profile across the range of other CVD risks.

For people at high risk of heart failure, however, CCBs do not appear to be cost effective. Diuretics are estimated to be the most cost-effective alternative for those at high risk of heart failure, provided that they do not also have a high risk of diabetes. For people with a high risk of both heart failure and diabetes, ACE inhibitors or ARBs may be the most cost-effective option. However, the applicability of the model to people under the age of 55 is uncertain, since it is based on trial data from mostly older people.

These results are sensitive to the cost of CCBs. The more expensive brands are not likely to be cost effective for use in the NHS. The results are also sensitive to the possible impact of drug

side effects. For groups or individuals expected to have significant side effects from CCBs, ACEi/ARBs or thiazide-like diuretics might prove to be more cost effective. There is also considerable uncertainty about the size of some treatment effects, which translates into uncertainty about the relative cost effectiveness of the drugs.

Finally the model results are robust to changes in the estimated treatment costs and quality of life impacts of diabetes, heart failure and other CVD events. They are also robust to changes in the relative risks of secondary CVD events following unstable angina, MI or stroke and also to assumptions about rates of non-CVD-related deaths in this hypertensive cohort.

Sensitivity analysis

Table C15 Sensitivity analysis for annual CVD risk and age

	Men				Women			
%	55	65	75	85	55	65	75	85
0.5	£25,880	£15,530	£10,990	£10,460	£43,450	£20,350	£14,250	£11,610
1.0	£34,040	£16,330	£10,030	£9,820	£76,050	£23,210	£12,060	£10,510
2.0	£30,730	£12,250	£8,610	£8,780	£38,230	£13,490	£9,310	£8,860
3.0	£18,490	£9,990	£7,600	£7,960	£17,320	£9,770	£7,660	£7,680
5.0	£11,090	£7,580	£6,290	£6,790	£9,100	£6,630	£5,800	£6,120

Interpretation

CCBs remained the most cost-effective option for CVD risk levels above 1% (holding all other variables constant at their base-case values). The only time the results change is for 55- and 65-year-olds with CVD less than 1% where A is the preferred option with ICERs ranging between about £16,000 to about £26,000 for men. This also suggests that A could be cost effective in the young/low risk patients.

Table C16 Sensitivity analysis for annual diabetes risk (65-year-old 2% CVD risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)								
	Men				Women				
%	D	B	A	C	D	B	A	C	–
0	–	–	–	£239,520	–	–	–	–	1
1	–	–	–	£13,380	–	–	–	£14,920	2
2	–	–	–	£8,250	–	–	–	£7,340	2
3	–	–	–	£6,740	£60	–	£4,230	£11,490	3
4	£180	–	£2,730	–	£140	–	£2,780	£56,340	4
5	£240	–	£2,080	–	£200	–	£2,080	–	4

1 = A, B and C dominated by D or C has an ICER well above £30,000 per QALY.
2 = A and B dominated: C versus D.
3 = B dominated: A versus D and C versus A.
4 = B and C dominated: D versus NI and A versus D.

▷ Interpretation

The results are sensitive to this assumption. When diabetes was removed from the analysis (annual diabetes risk of 0%), D becomes the optimal choice dominating all other interventions, especially for women. CCBs remained the most cost-effective option at all levels of diabetes greater or equal to 1% and up to 3% annual diabetes risk (holding all other variables constant at their base case values). Above 3% annual diabetes risk, ACE/ARB combination becomes the most cost-effective option when compared with D. C is dominated by A combination. As the annual diabetes risk increased, the ICERs for C versus D become more favourable, since C does better in preventing diabetes than D, however ACE/ARB does much better than C, hence it becomes cost effective at higher incidence levels.

Table C17 Sensitivity analysis for relative risk of CVD events with diabetes

	Incremental cost-effectiveness ratios (£ per QALY)														
	Annual risk of diabetes = 1.1%					Annual risk of diabetes = 2%					Annual risk of diabetes = 4%				
	D	B	A	C		D	B	A	C		D	B	A	C	
0.5	£10	–	–	–	0	£130	–	–	–	0	£350	–	–	–	0
1	–	–	–	£36,420	1	£100	–	–	£20,930	2	£300	–	–	£11,180	2
2	–	–	–	£12,250	1	£30	–	–	£7,070	2	£180	–	£2,730	–	4
4	–	–	–	£7,790	1	–	–	£3,900	–	3	–	–	£1,840	–	3

0 = A, B and C dominated by D: D versus NI.
1 = A and B dominated: C versus D.
2 = A and B dominated: D versus NI and C versus D.
3 = B and C dominated: A versus D.
4 = B dominated: D versus NI and A versus D.

▷ Interpretation

The results are sensitive to the relative risk of CVD events for people with diabetes. For a given level of diabetes risk, the cost effectiveness of CCBs improves as the relative risk of CVD events for people with diabetes increases. It is more cost effective to treat with ACEi/ARB than CCB at higher levels of diabetes risk if the relative risk of CVD events is also high. When the relative risk of CVD events for people with diabetes is less than 1, D becomes the optimal choice even at higher annual incidence of diabetes.

Table C18 Sensitivity analysis for relative risk and incidence of CVD events following heart failure (65-year-old 2% CVD risk, 1.1% diabetes risk)

	Incremental cost-effectiveness ratios (£ per QALY)														
	Annual risk of HF = 1%					Annual risk of HF = 2%					Annual risk of HF = 4%				
	D	B	A	C		D	B	A	C		D	B	A	C	
0.5	–	–	–	£9,550	1	–	–	–	£52,200	1	–	–	–	–	2
1	–	–	–	£12,250	1	–	–	–	–	1	–	–	–	–	2
2	–	–	–	£17,920	1	–	–	–	–	2	–	–	–	–	2
4	–	–	–	£30,220	1	–	–	–	–	2	–	–	–	–	2

1 = A and B dominated: C versus D.
2 = D dominates all other interventions.

▷ Interpretation

The results are sensitive to the relative risk of CVD events for people with heart failure. If the annual relative risk of heart failure is less than 1, and the annual incidence is set at 1%, C remains the most cost-effective option. As the relative risk of CVD events after heart failure increases to 1% and beyond and the annual incidence rises to 2% and above, D becomes the optimal choice. This suggests that for patents with hypertension with heart failure D could be the drug of choice.

Table C19 Sensitivity analysis for incidence of CVD events following a stroke (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

Relative risk of CVD events with stroke *	Incremental cost-effectiveness ratios (£ per QALY)								
	Men				Women				
	D	B	A	C	D	B	A	C	
0.2	–	–	–	£13,650	–	–	–	£17,910	1
0.5	–	–	–	£12,750	–	–	–	£14,440	1
1	–	–	–	£12,250	–	–	–	£13,490	1
2	£10	–	–	£11,960	–	–	–	£12,960	1

1 = A and B dominated: C versus D. * Compared with CVD event risks in baseline model.

▷ Interpretation

The results are not sensitive to the incidence of CVD events following a stroke. CCB remains the most cost-effective option, even if these incidences are only a fifth of the values assumed in the base case analysis.

Table C20 Sensitivity analysis for relative risk of non-CVD death (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)								
Relative risk non-CVD death *	Men				Women				
	D	B	A	C	D	B	A	C	
1%	–	–	–	£12,250	–	–	–	£13,490	1
2%	–	–	–	£7,240	–	–	–	£7,970	1
4%	£50	–	–	£5,350	–	–	–	£5,850	2
8%	–	£130	–	£4,220	£30	–	–	£4,630	2

1 = A and B dominated: C versus D.
2 = A and B dominated: D versus NI and C versus D.
* Compared with general population.

▷ Interpretation

The results are not sensitive to changes in the assumptions about the relative risk of death from non-CVD in the hypertensive cohort compared with the general population. Hypertensive treatment remains highly cost-effective, and CCBs remain the preferred option (holding all other variables at their base case values).

Table C21 Sensitivity analysis for efficacy of treatment (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)									
	Lower limit of treatment effect					Upper limit of treatment effect				
	D	B	A	C		D	B	A	C	
D versus NI	–	–	–	£9,690	1	–	–	–	£18,800	1
C versus D	–	–	£2,230	£2,600	2	–	–	–	–	3
B versus C	–	–	–	£12,250	1	–	£5,980	£7,940	–	4
ACEi versus C	–	–	£2,850	–	5	–	–	–	£12,250	1
ARB versus B	–	–	£5,430	–	5	–	–	–	£12,250	1

1 = A and B dominated: C versus D.
2 = B dominated: A versus D and C versus A.
3 = D dominates all.
4 = C dominated: B versus D and A versus B.
5 = B and C dominated: A versus D.

▷ Interpretation

1 The results are not sensitive to the treatment effect of diuretics compared with no intervention. CCBs remained the most cost-effective option when the relative risks for diuretics were varied between the lower and upper 95% confidence limits from the meta-analysis, ICERs ranged between about £10,000 for the lower CI and about £19,000 per QALY for the upper CI.

2 The results are sensitive to the treatment effect of CCBs compared with diuretics. When the relative risks of CCBs were increased to the upper 95% confidence limits, diuretics dominated all other interventions.

3 When the relative risks for CCBs compared with BBs were increased to their upper 95% limits, BB was no longer dominated. A became the most cost-effective option compared with the next most cost-effective option – option B, with an ICER of about £7,900 per QALY. C was dominated by A.

4 ACEi/ARBs became the most cost-effective option when the relative risks for ACEi compared with CCBs were reduced to their lower limits. In this case their ICER compared with diuretics was around £3,000 per QALY and they dominated CCBs.

5 The results were sensitive to the treatment effects from the ARB versus BB comparison. When the relative risks of ARBs compared with BB were reduced to their lower limits, the ACEi/ARB became the most cost-effective option, with an ICER of around £5,000 per QALY gained.

Table C22 Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% HF risk) (Scenario 1: BB versus DD)

	Incremental cost-effectiveness ratios (£ per QALY)									
	Lower limit of treatment effect					Upper limit of treatment effect				
	D	B	A	C		D	B	A	C	
D versus D	–	£1,210	–	–	1	–	–	–	£12,250	3
ARB versus B	–	–	£4,630	–	2	–	–	–	£12,250	3

1 = A and C dominated: B versus D.
2 = B and C dominated: A versus D.
3 = B and A dominated: C versus D.

▷ Interpretation

1 The results do not change if the treatment effects for BB are taken from the mean relative risks in comparison with diuretics (rather than compared with CCB as in the base case model). BBs remain dominated and CCBs are the most cost-effective option in this case. If the lower limits of the confidence intervals for BB compared with diuretics are used, BB appear to be the most cost-effective option with an estimated ICER of about £1,200.

2 If the lower limits of the confidence intervals for ARB compared with BB are used, ACE/ARB becomes the most cost-effective option with an ICER of about £4,600/QALY. CCBs are dominated. If upper confidence limit are used the base results do not change.

Table C23 Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% HF risk) (Scenario 2: ACEi versus DD)

	Incremental cost-effectiveness ratios (£ per QALY)									
	Lower limit of treatment effect					Upper limit of treatment effect				
	D	B	A	C		D	B	A	C	
ACEi versus DD	–	–	£3,660	–	1	–	–	–	£12,250	2

1 = B and C dominated: A versus D.
2 = A and B dominated: C versus D.

▷ Interpretation

The results also do not change if the treatment effects of ACEi are based on their mean relative risks compared with diuretics, rather than with CCBs as in the baseline model. However, the ACEi/ARB combination appears to be the most cost-effective option if the lower confidence intervals for the effects of ACEi versus diuretics are used.

Table C24 Sensitivity analysis, percentage of ARBs used in conjunction with ACEi (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)							
	Men				Women			
% of ARBs	D	B	A	C	D	B	A	C
0	–	–	–	£12,250	–	–	–	£13,490
10	–	–	–	£12,250	–	–	–	£13,490
15	–	–	–	£12,250	–	–	–	£13,490
20	–	–	–	£12,250	–	–	–	£13,490
25	–	–	–	£12,250	–	–	–	£3,920
50	–	–	£27,090	£12,250	–	–	£36,200	£3,920
60	–	–	£20,950	£12,250	–	–	£24,830	£3,920
70	–	–	£18,520	£12,250	–	–	£21,010	£3,920
80	–	–	£17,210	£12,250	–	–	£19,090	£3,920
90	–	–	£16,380	£12,250	–	–	£17,920	£3,920
100	–	–	£15,810	£12,250	–	–	£17,130	£3,920

▷ Interpretation

The model is sensitive to assumptions about the number of patients who cannot tolerate ACEs and switch to ARBs. CCBs remained the most cost-effective option, as long the ACEi/ARB ratio was less than 50%. 50% or more of ARB use results in A (ACEi/ARB) option being cost effective when compared with CCB. The ICER when A is compared with the next most cost-effective option (C) varied from about £16,000 to about £19,000 per QALY gained, when 70% or more of ARBs were used. As the percentage use of ARB increased, the ACEi/ARB option became more cost effective with ICER falling to about £16,000 when ARB was used (100%).

Table C25 Sensitivity analysis for cost of drugs (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% HF risk) (cheapest and most expensive)

	Incremental cost-effectiveness ratios (£ per QALY)							
	Men				Women			
	D	B	A	C	D	B	A	C
Cheapest	–	–	–	£6,320	–	–	–	£6,780
Most expensive	£680	–	–	£37,840	£600	–	–	£42,460

▷ Interpretation

The model is sensitive to assumptions about the cost of drugs. CCBs remained the most cost-effective option: when the cheapest drugs are used the ICER for CCB improves, falling to about £6,300 for men. When the most expensive drugs are used the ICERs increase to a level above what is usually considered affordable by the NHS, between £20–30,000 per QALY, making D the optimal choice. However, this is an unlikely scenario since the price of all hypertensive medication is off patent and thus is falling.

Table C26 Sensitivity analysis for costs of events (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)							
	Lower limit of costs (50% reduction)				Upper limit of costs (double the costs)			
	D	B	A	C	D	B	A	C
No event	–			£12,130	£220			£12,500
Unstable angina 1	–			£12,230	–			£12,300
Unstable angina subs	–			£12,210	–			£12,340
Acute MI	–			£12,150	–			£12,450
MI subs	–			£12,170	–			£12,410
Diabetes	–			£12,320	–			£12,120
Stroke 1	£110			£12,440	–			£11,870
Stroke subs	–			£12,270	–			£12,210
Heart failure	£30			£11,860	–			£13,030
HF subs	£40			£11,630	–			£13,510

Interpretation

CCBs remained the most cost-effective option when assumptions about the costs of events are changed. When the costs of events are reduced by 50% one at a time holding other events constant, CCB remained cost effective when compared with the next most cost effective alternative (D). When costs of events were doubled, CCB remained the optimal choice. The model is robust to assumptions about costs of events with ICERs falling below £14,000 per QALY when costs are either halved or doubled.

Table C27 Sensitivity analysis for quality of life loss from hypertensive treatment (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

% reduction of quality of life with treatment	Incremental cost-effectiveness ratios (£ per QALY)									
	Men					Women				
	D	B	A	C	D	B	A	C		
0	–	–	–	£12,250	1	–	–	–	£13,490	1
1	–	–	–	£12,250	1	–	–	–	£13,490	1
2	–	–	–	£12,250	1	–	–	–	£13,490	1
3	–	–	–	£12,250	1	–	–	–	£13,490	1
4	–	–	–	–	2	–	–	–	–	2
5	–	–	–	–	2	–	–	–	–	2

1 = A and B dominated: C versus D.
2 = A, B and C dominated: NI versus D.

▷ Interpretation

The base case model assumes there is no loss in quality of life as a result of hypertensive treatment side effects. Assuming that treatment results in a reduction in quality of life of up to 3%, the results do not change. However, if the loss of quality of life due to the side effects of hypertensive treatment is assumed to be 4% or greater, then treatment may not be cost effective. This assumes equal quality of life loss for all drugs, which is unlikely given that we know that there are differing rates of adverse events and withdrawals.

Table C28 Sensitivity analysis for quality of life with CCBs and ACEi/ARBs (65-year-old man, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

	Incremental cost-effectiveness ratios (£ per QALY)															
% reduction of quality of life with CCBs	0% reduction in QoL with ACEi/ARBs				0.2% reduction in QoL with ACEi/ARBs				0.4% reduction in QoL with ACEi/ARBs				0.6% reduction in QoL with ACEi/ARBs			
	D	A	C		D	A	C		D	A	C		D	A	C	
0.1	–	-	£18,460	1	–	–	£18,460	1	–	–	£18,460	1	–	–	£18,460	1
0.2	–	£26,710	–	1	–	–	£37,390	1	–	–	£37,390	1	–	–	£37,390	1
0.4	–	£26,710	–	2	–	–	–	3	–	–	–	3	–	–	–	3
0.8	–	£26,710	–	2	–	–	–	3	–	–	–	3	–	–	–	3
1.0	–	£26,710	–	2	–	–	–	3	–	–	–	3	–	–	–	3
2.0	–	£26,710	–	2	–	–	–	3	–	–	–	3	–	–	–	3

1 = A and B dominated: C versus D.
2 = B and C dominated: A versus D.
3 = D dominates all.

▷ Interpretation

Small differences in adverse effects of the different drugs may change their relative cost effectiveness. Holding all other parameters constant at their base case values, A becomes the most cost-effective option if CCBs treatment results in a 0.2% loss in quality of life due to adverse effects. For comparison, the quality of life impact of chronic lower extremity oedema has been estimated at 10% (Harvard CEA Registry[75]). Thus, if an individual experiences even minor or infrequent side effects with CCBs, then alternative antihypertensive treatment may be more cost effective. If ACEi/ARB treatment is well tolerated, with minimal impact on quality of life due to side effects, then it is estimated to be the most cost-effective alternative to CCBs. However, if ACEi/ARB treatment also leads to a relatively modest loss of quality of life (of about 0.2%) combined with about 0.2% loss due to CCBs, then diuretics become a more cost-effective alternative. See above for details of the magnitude of change.

Table C29 Sensitivity analysis for quality of life loss from CVD events and diabetes (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

Quality of loss of life	Incremental cost-effectiveness ratios (£ per QALY)									
	Lower limit					Upper limit				
	D	B	A	C		D	B	A	C	
UA (0.7–0.9)	–	–	–	£12,270	1	–	–	–	£12,230	1
MI (0.7–0.9)	–	–	–	£12,280	1	–	–	–	£12,200	1
Diabetes (0.8–1)	–	–	–	£12,090	1	–	–	–	£12,420	1
Stroke (0.5–0.7)	–	–	–	£12,200	1	–	–	–	£12,280	1
Heart failure (0.6–0.8)	–	–	–	£12,600	1	–	–	–	£11,980	

1 = A and B dominated: C versus D.

▷ Interpretation

The results are not sensitive to changes in the assumed quality of life loss or increase due to CVD events or the onset of diabetes. CCB remained the most cost-effective option under all scenarios tested.

Table C30 Sensitivity analysis for increased effectiveness of A/B for younger patients (45-year-old, 2% CVD risk, 1.1% diabetes risk, 1% HF risk)

% improvement in effects of A/B	Incremental cost-effectiveness ratios (£ per QALY)									
	Men					Women				
	D	B	A	C		D	B	A	C	
1	£10	–	£37,140	–	1	£30	–	£76,500	–	1
2	£10	–	£13,110	–	1	£30	–	£15,950	–	1
3	£10	–	£7,950	–	1	£30	–	£8,900	–	1
4	£10	–	£5,700	–	1	£30	–	£6,170	–	1
10	£10	–	£2,100	–	1	£30	–	£2,160	–	1
12	£10	–	£1,730	–	1	£30	–	£1,770	–	1

1 = B and C dominated: D versus NI, A versus D.

▷ Interpretation

The model is not designed to estimate cost effectiveness for a younger population, since most of the evidence about treatment effects derives from studies in older people. However, the model was used to test the possible impact of improved performance of ACEi, ARBs and BBs in a younger group. Taking the predicted baseline effects of a 45 year old cohort (at 2% annual CVD risk and 1.1% annual diabetes risk and 1% heart failure risk), cost effectiveness estimates were made for given percentage improvements in treatment effects for ACEi/ARB and BB compared with the meta analysis figures. For 45 year old men/women an improvement of more than 1 percentage point makes ACEi/ARB the optimal treatment. However, beta blockers were still dominated even at higher percentage improvements, assuming an equal percentage improvement of ACEi/ARBs and BBs for this younger population. This analysis does lend some support to the hypothesis that ACEi/ARBs may be more cost effective than CCBs in younger patients.

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