Appendix I: Cost-effectiveness analysis – pharmacological treatment (updated 2011)

I.1 Introduction

This model was developed as part of the 2006 pharmacological update (CG34) to balance clinical outcomes and to test the cost effectiveness of different initial antihypertensive medications. As part of the 2011 update this analysis was rerun with updated costs. The relative risks for ARBs were also updated based on new ACEi vs ARB data. The methods and results below have been updated to reflect the revisions to the analysis. A summary of the overall impact of the update compared to the previous analysis is given after the results section.

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I.2 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.

I.3 Methods

I.3.1 Population and subgroups

The model considered patients with essential hypertension seen in primary care, excluding those with pre-existing cardiovascular disease (CVD), heart failure 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 basecase analysis presented below shows the results for 65-year-old men and women with 2% CVD risk, 1% heart failure risk and 1.1% diabetes risk. Sensitivity analysis are also presented showing whether and how the results vary by age, sex, CVD, heart failure and diabetes risk.

The model is based on trial evidence that included relatively few younger (under 55) or black people of African and Caribbean descent, 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 people (under 45).

I.3.2 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)
- angiotensin-converting enzyme inhibitors (ACEis) / angiotensin-II receptor blockers (ARBs) (A).

At basecase, it was assumed that 80% of patients will be on ACEis and 20% will be on ARBs, because of some people's inability to tolerate ACEis (expert opinion). ACEi/ARBs were combined as a strategy as they were considered to have equivalent effectiveness. 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.

I.3.3 Outcomes

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

The only side effects modelled were onset of heart failure and diabetes. Other side effects were not modelled in the basecase 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.

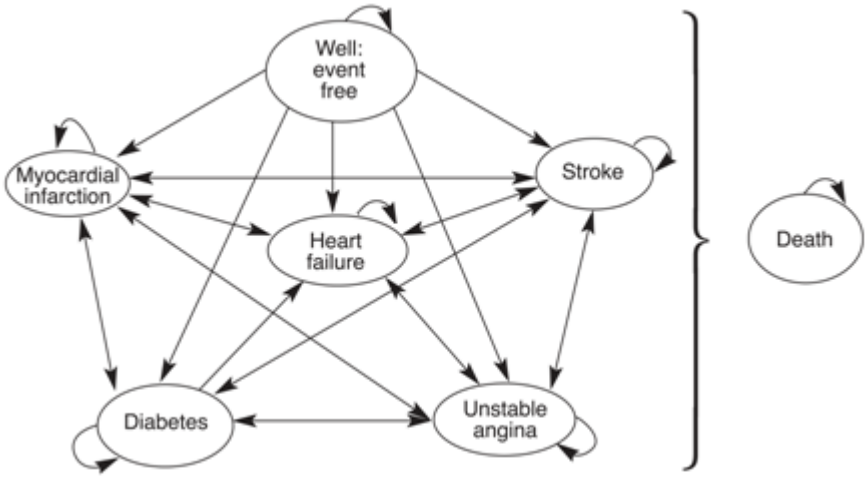
Health outcomes for the cost-effectiveness analysis are summarised in the form of quality-adjusted life-years (QALYs), where one QALY represents one year of healthy life.

I.3.4 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 118 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 118: Model structure for hypertension(a)



a) Arrows represent the possible transitions between each of the health states

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, heart failure risk and diabetes risk. For illustration, the equivalent annual transition probabilities for untreated 65-year-old men and women with 2% CVD, 1% heart failure risk and 1.1% diabetes risk are shown in Table 82 and Table 83. Unless better data for a hypertensive population were available, the probabilities were based on those used in an analysis of the cost effectiveness of statins developed by the University of Sheffield's School of Health and Related Research (ScHARR) for the NICE technology appraisal[625]. The GDG advised on this and other data used in the model.

Table 82: 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[625]
Well to MI	0.0035	Statins model[625]
Well to diabetes	0.0110	ASCOT trial[157]
Well to stroke	0.0054	Statins model[625]
Well to heart failure	0.0098	SHEP[483]
Well to death	0.0180	Statins model and population life tables[625]
Unstable angina to MI	0.0300	Statins model[625]
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 heart failure	0.0230	Assumed to be the same as MI to heart failure
Unstable angina to death	0.0348	Statins model and population life tables[625]
MI to unstable angina	0.0078	HOPE[25]
MI to MI	0.0721	Statins model[625]
MI to diabetes	0.0067	HOPE[25]
MI to stroke	0.0095	Statins model[625]
MI to heart failure	0.0230	HOPE[25]
MI to death	0.0258	Statins model and population life tables[625]
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

Parameter	Annual probability (%)	Source
Diabetes to stroke	0.0108	Double the risk of the well population
Diabetes to heart failure	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[625]
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model[625]
Stroke to heart failure	0.0115	Assumed to be half of MI to heart failure
Stroke to death	0.3548	Statins model and population life tables[625]
Heart failure to unstable angina	0.0230	Assumed to be the same as heart failure to MI
Heart failure to MI	0.0230	SOLVD[12]
Heart failure to stroke	0.0103	SOLVD[12]
heart failure to heart failure	0.0545	SOLVD[12]
Heart failure to death	0.0768	SOLVD and population life tables[12]

Table 83: 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[625]
Well to MI	0.0024	Statins model[625]
Well to diabetes	0.0110	ASCOT trial[157]
Well to stroke	0.0076	Statins model[625]
Well to heart failure	0.0098	SHEP[483]
Well to death	0.0141	Statins model and population life tables[625]
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 heart failure	0.0230	Assumed to be the same as MI to heart failure
Unstable angina to death	0.0307	Statins model and population life tables[625]
MI to unstable angina	0.0078	HOPE[25]
MI to MI	0.0721	Statins model[625]
MI to diabetes	0.0067	HOPE[25]
MI to stroke	0.0095	Statins model[625]
MI to HF	0.0230	HOPE[25]
MI to death	0.0217	Statins model and population life tables[625]
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 heart failure	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[625]
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model[625]
Stroke to heart failure	0.0115	Assumed to be half of heart failure to MI

Parameter	Annual probability (%)	Source
Stroke to death	0.3507	Statins model and population life tables[625]
Heart failure to unstable angina	0.023	Same as MI to heart failure
Heart failure to MI	0.023	SOLVD[12]
Heart failure to stroke	0.0103	SOLVD[12]
Heart failure to heart failure	0.0545	SOLVD[12]
Heart failure to death	0.0727	SOLVD and population life tables[12]

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 heart failure 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 a lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

I.3.5 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 84. 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[24]). 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[157]. The incidence of heart failure in the baseline model (0.98%) was taken from the placebo arm of the SHEP trial[483].

Table 84: 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[625].					
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					

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 85) was taken from 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[457]. 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 a sensitivity analysis LC = lowest cost option; '-' = option ruled out by simple or extended dominance

** 1 = A and B dominated: C versus D*

*** Relative risk of CVD event following stroke compared with CVD event risks for people who have not had a CVD event*

Risk of non-CVD death

As shown in Table 105, conclusions 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 105, raising the cohort's relative risk from 1 to 8.

Table 85: Baseline non-cardiovascular disease related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales						
Age	**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[457]						
All cause mortality, estimated from life tables, 2002–04, England and Wales						
Age	**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[458]		
Estimated non-circulatory deaths for hypertensive cohort		
Age	**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%

The risk of secondary or subsequent events, following unstable angina, MI, stroke or heart failure are shown in Table 86. 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)[642] noted that the increase in CVD risk in men is twice, while in women it is four-fold. This assumption was tested in a sensitivity analysis. Probabilities of having unstable angina, heart failure and diabetes after an MI were taken from HOPE[25], 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, heart failure and CVD death following onset of heart failure were taken from the placebo arm of the SOLVD trial[12]. Because of a lack of data, it was also assumed that transitions from UA to diabetes, heart failure 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 heart failure following a stroke is half that following MI.

Table 86: 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[625]
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.00950	Assumed same as MI to stroke
	Heart failure	0.02300	Assumed same as MI to heart failure
	CVD death	0.02000	Statins model[625]
MI	UA	0.00775	HOPE[25]
	MI	0.07210	Statins model[625]
	Diabetes	0.00667	HOPE[25]
	Stroke	0.00950	Statins model[625]
	Heart failure	0.02300	HOPE[25]
	CVD death	0.01100	Statins model[625]
Stroke	UA	0.00160	Assumed same as for stroke to MI
	MI	0.00160	Statins model[625]
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.28750	Statins model[625]
	Heart failure	0.01150	Assumed half rate for MI to heart failure
	CVD death	0.34000	Statins model[625]
Heart failure	UA	0.02300	SOLVD[12]

After	Transition to	Annual risk	Source
	MI	0.02300	SOLVD[12]
	Stroke	0.01025	SOLVD[12]
	Heart failure	0.05450	SOLVD[12]
	CVD death	0.06200	SOLVD[12]

I.3.6 Treatment effects

The relative treatment effects of these interventions were taken from the meta-analysis of head-to-head studies done for the 2006 guideline update (except for the ACEi versus ARB data that was taken from a meta analysis of studies in the 2011 update[552,587,653]. 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, C versus ACEi, and ACEi versus ARB (Table 87). Sensitivity analyses were conducted for two other scenarios: firstly by replacing the estimate for B with a comparison with D (Table 88) and secondly by replacing the estimate for ACEis with a comparison with D (Table 89).

Table 87: Relative risks of drugs versus no treatment (basecase analysis)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984	1.01
MI	0.780	0.796	0.855	0.85
Diabetes	0.985	0.808	1.137	0.77
Stroke	0.690	0.656	0.851	0.69
Heart failure	0.530	0.731	0.761	0.65
Death	0.910	0.883	0.939	0.90

Table 88: Relative risks of drugs versus no treatment (scenario 1: B versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984 *	1.01
MI	0.780	0.796	0.835	0.85
Diabetes	0.985	0.808	1.138 *	0.77
Stroke	0.690	0.656	0.794	0.69
Heart failure	0.530	0.731	0.762 *	0.65
Death	0.910	0.883	0.901	0.90
* Based on B versus C comparison, since B versus D were not available for this outcome.				

Table 89: Relative risks of drugs versus no treatment (scenario 2: ACEi versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984	1.01
MI	0.780	0.796	0.855	0.90
Diabetes	0.985	0.808	1.138	0.85
Stroke	0.690	0.656	0.851	0.64
Heart failure	0.530	0.731	0.762	0.72
Death	0.910	0.883	0.939	0.84

I.3.7 Cost data

The NICE reference case[430] 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. As per current NICE guidance[430], 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 90. Event costs reviewed as part of the diagnosis model undertaken for the 2011 update were updated on the same basis (stroke, MI, unstable angina) adjusted for the 6-month cycle length of this model (see 'Appendix J: Cost-effectiveness analysis – blood pressure monitoring for confirming a diagnosis of hypertension (new 2011)' for details). Other event costs were simply inflated to 2009/10 costs (diabetes, heart failure).

Costs for stroke and post-stroke were based on Youman et al.[649] (these were also used in the NICE Statins health technology assessment (HTA)[625]). 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[48]. Acute MI costs are based on those reported by Palmer et al. (also utilised in the Statins HTA) this included costs for revascularisation. Post-MI costs are based on an estimate made by the 2004 GDG for the hypertension guideline. Initital and subsequent costs for unstable angina were assumed to be 60% of the costs for MI. Heart failure costs were taken from NHS reference costs. It was assumed that people with no event had an annual GP check-up (as recommended in the guideline). A check-up was estimated to cost £28 based on the average UK cost of a GP appointment[486].

Costs were inflated to 2009/10 prices using the Personal Social Services Research Unit (PSSRU), Unit Costs of Health and Social Care 2010 inflation indices[486].

Table 90: Costs of health states

Health state	Cost per 6-month cycle	Source
MI	£4,933	Palmer 2004[474] inflated to 2009/10[486]
Post-MI costs	£282	NICE Hypertension guideline 2004[441] inflated to 2009/10[486]
Unstable angina	£2,960	Assumed 60% of MI cost.
Subsequent unstable angina costs	£169	Assumed 60% of post-MI cost.
Diabetes	£455	Ara 2004[48] inflated to 2009/10[486]
Stroke	£10,190	Youman et al.[649] inflated to 2009/10[486]
Post-stroke costs	£1,119	Youman et al.[649] inflated to 2009/10[486]
Heart failure	£2,649	NHS reference costs 2005/06 inflated to 2009/10[486]
Post-heart failure costs	£282	Assumed to be same as post MI
Death	£0	
No event	£28	

Drug costs were calculated based on the prices quoted in the British National Formulary 60 (September 2010) based on the optimal dose for hypertension[306]. Optimal doses were provided by clinical members of the GDG. In the base-case analysis, the non-proprietary cost for the most commonly used drug in each class (as based on the 2008 NHS Prescription Cost Analysis[593]) was used. The exception was for ARBs where losartan was used in the base-case analysis as it has recently come off patent and so is now considerably cheaper than other drugs in the class and therefore likely

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to be more commonly prescribed in the future than historically. The impact of using the cheapest and most expensive drug in each class was also tested in sensitivity analyses. Drug costs used are summarised in Table 91.

Table 91: Drug costs per year

	Used in basecase analysis	Cheapest drug	Most expensive drug
ACEi	Ramipril (10mg): £20.73	Ramipril (10mg): £20.71	Cilaipril (5mg): £163.08
ARB	Losartan (100mg): £25.94	Losartan (100mg): £25.94	Valsartan (320mg): £263.71
B	Atenolol (100mg): £13.17	Atenolol (100mg): £13.17	Acebutolol (800mg): £485.45
C	Amlodipine (10mg): £18.64	Amlodipine (10mg): 18.64	Isradipine (10mg): £431.22
D	Bendroflumethiazide (2.5mg): £11.86	Bendroflumethiazide (2.5mg): £11.86	Xipamide (20mg): £50.74
The cost of diuretics are also analysed in a further sensitivity analysis using the cost for: chlortalidone (50mg(a)): £19.81; indapamide (2.5mg): £16.03.			

a) 25mg was considered the optimal dose but a cost for this tablet size was not listed in the BNF.

Source: British National Formulary 60, September 2010[306]

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I.3.8 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 Table 92 and Table 93. An extensive literature search was conducted during the development of the statins HTA model to identify the best available utility estimates for the various health states[625]. Thus estimates for MI, unstable angina and stroke were taken from the statins HTA. Diabetes and heart failure estimates were taken from the Cost-Effectiveness Analysis (CEA) Registry[264]. For MI and unstable angina a higher utility was applied after the initial 6 months. For diabetes, stroke and heart failure a constant utility from onset of the condition was assumed.

Table 92: Health state utility weights

Health state	Utility weight	Source
MI (first 6 months)	0.76	Statins model[625]
Post MI	0.88	Harvard CE Registry[264]
Unstable angina (first 6 months)	0.77	Statins model[625]
Post unstable angina	0.80	Assumption
Stroke	0.63	Statins model[625]
Diabetes	0.90	Harvard CE Registry[264]
Heart failure	0.71	Harvard CE Registry[264]
Death	0.00	Statins model[625]

Table 93: Utility weight by age

Age group	Age utility weight	Source
45–54	0.85	DH Health Survey for England 1996[24]
55–64	0.79	DH Health Survey for England 1996[24]
65–74	0.78	DH Health Survey for England 1996[24]
75+	0.73	DH Health Survey for England 1996[24]
DH = Department of Health.		

As in the Statins model[625], utilities were adjusted to reflect the fact that health-related quality of life in the general population decreases with age (that is, multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996)[24].

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[129,160,161,218,278,598,607,662]. 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[264]). Where these have compared different antihypertensive medications, they have generally assumed equal utility loss from adverse effects of treatment[301,307]. 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[166]. 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[412] 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 basecase model. However, we did a sensitivity analysis to investigate how large any such effects would have to be to change the results.

I.4 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).

$$\text{ICERs} = \frac{\text{Cost of X} - \text{Cost of Y}}{\text{QALY of X} - \text{QALY of Y}}$$

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 (cheapest indicated by LC (lowest cost) in the results tables below).
2. If a drug is more expensive and less effective than the previous one, then it is said to be ruled out by 'simple dominance' and is excluded from further analysis (indicated by a dash '-' in the results tables below).
3. 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' (indicated by a dash '-' in the results tables below).
4. ICERs are recalculated excluding any drugs subject to dominance or extended dominance (these ICERs are given in the results tables below).

I.5 Sensitivity analysis

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

I.6 Results

I.6.1 Base-case results

The base-case results are presented in Table 94 for 65-year-old men and women with an annual CVD risk of 2%, heart failure 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 class in this group is calcium-channel blockers (C). The ICER of C compared with thiazide-type diuretics (D) is £1,520 to £1,960 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, A and C are estimated to be cheaper and more effective. This is illustrated in Figure C2, since B lies to the northwest of D, A and C. 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 119, A lies to the northwest of a straight line joining points D and C. However, it should be noted that the absolute differences between A, C and D are small.

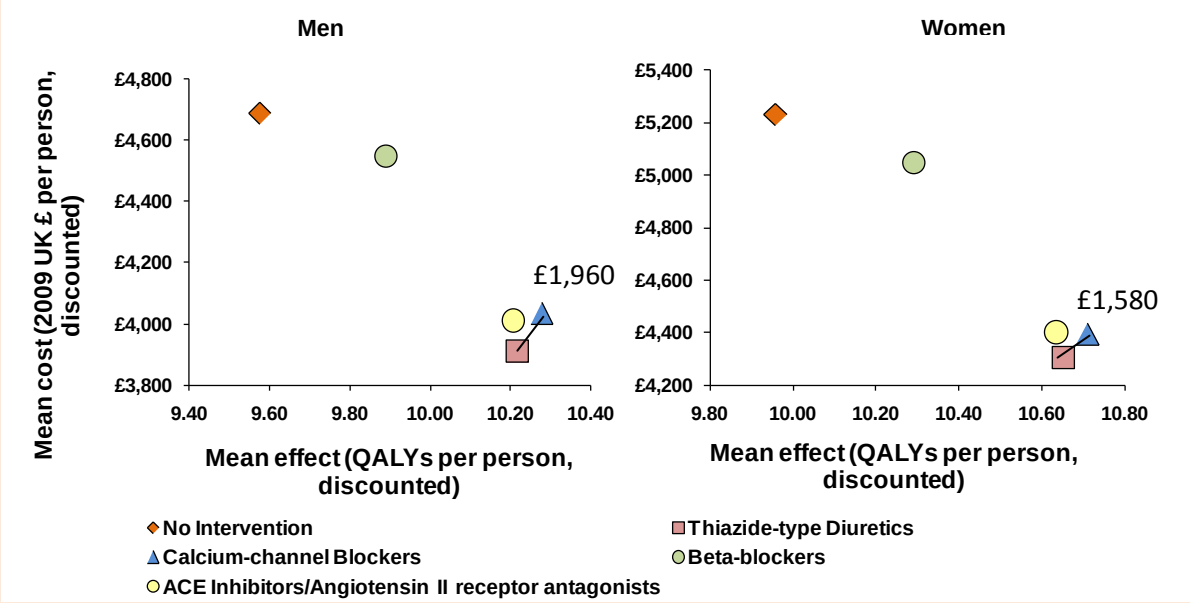
Table 94: 2011 base-case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% heart failure risk)

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

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Update 2011

Figure 119: 2011 base-case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% heart failure risk)

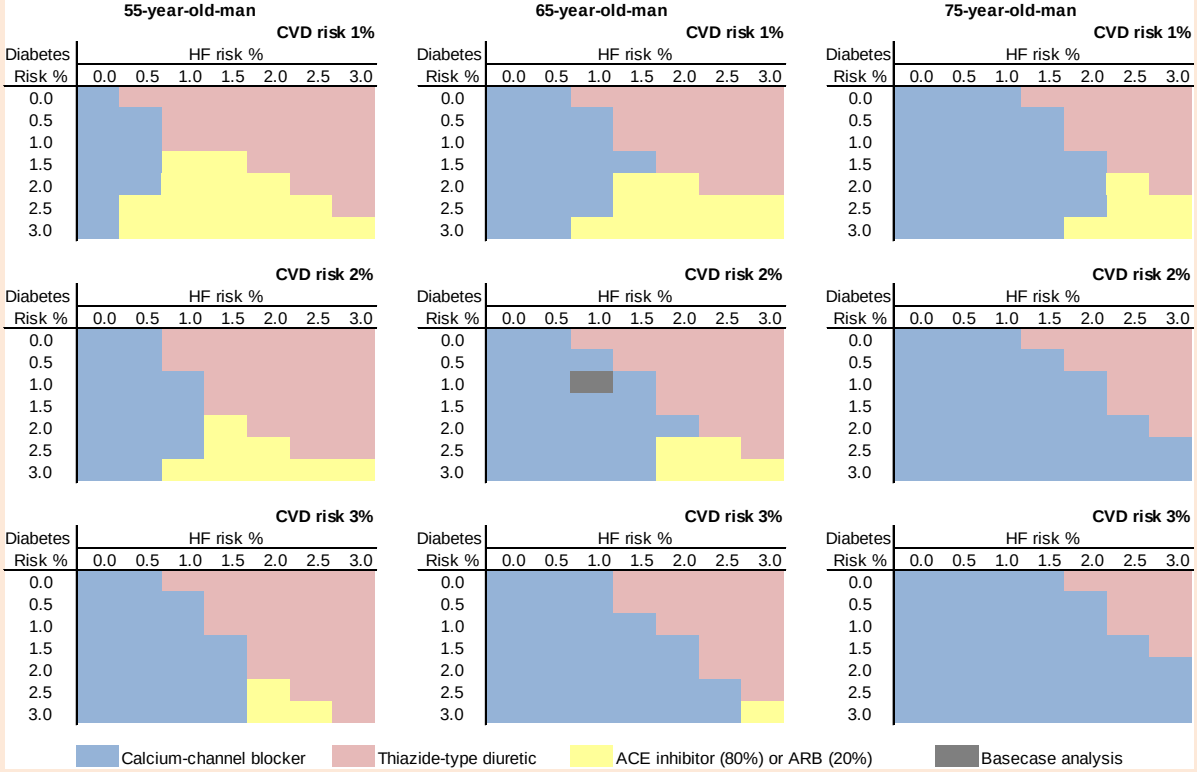


I.6.2 Results for patient subgroups

Figure 120 and Figure 121 show how cost effectiveness varies with age, sex, annual CVD risk, annual diabetes risk and annual heart failure risk, based on a cost-effectiveness threshold of £20,000 per QALY. The meta-analysis found that thiazide-type diuretics and CCBs have similar effects on the incidence of MI, stroke and death (Chapter 12). 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 people over 55 years of age at relatively low risk of heart failure and for those at relatively high risk of diabetes. The GDG noted that in a 55 year old the upper rates of heart failure and diabetes explored in the analysis were extremely unlikely.

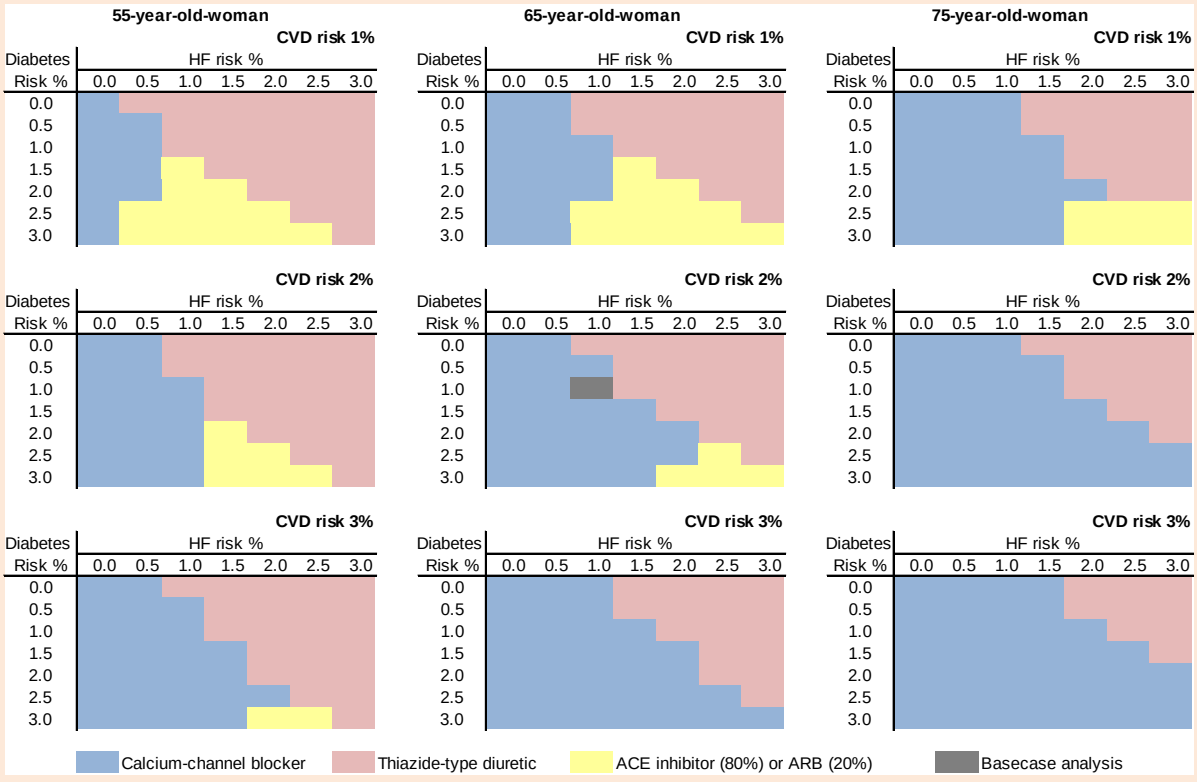
A appear to be a cost-effective alternative to C at high levels of diabetes risk and intermediate levels of heart failure risk. This is because they are associated with lower rates of heart failure and diabetes, but higher rates of stroke.

Figure 120: Four-way sensitivity analysis: most cost-effective (represented by colour) first-line drug for men by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year



ARB = angiotensin-II receptor blocker; CVD = cardiovascular disease; HF = heart failure;

Figure 121: Four-way sensitivity analysis: most cost-effective first-line drug for women by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year.



ARB = angiotensin-II receptor blocker; CVD = cardiovascular disease; HF = heart failure;

Update 2011

In addition, as Table 95 shows, when CVD is 0.5% (holding all other variables constant at their base-case values, for men and women age 55 A becomes the preferred option. This suggests that A could be cost effective in in the young/low risk people.

Table 95: Sensitivity analysis for annual CVD risk and age (1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios of most effective (highest QALYs) option								
	MEN				WOMEN			
Annual CVD risk	Age							
	55	65	75	85	55	65	75	85
0.5%	A dominant	£5,370	£2,350	£2,240	A dominant	£12,440	£2,800	£2,330
1.0%	£16,860	£2,950	£2,000	£1,970	£3,750*	£3,490	£2,090	£1,860
2.0%	£4,000	£1,960	£1,510	£1,530	£3,200	£1,520	£1,210	£1,170
3.0%	£2,210	£1,430	£1,170	£1,190	£1,050	£800	£700	£680
5.0%	£1,180	£900	£740	£730	£260	£230	£160	£70

*All ICERs above are for C apart from * where ICER is for D*

Update 2011

I.6.3 Younger people

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 ACEis, 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 was estimated for given percentage improvements in treatment effects for ACEi/ARB and BB compared with the meta-analysis figures.

Diuretics appear to be the most cost-effective option for this age group in the base-case analysis, as shown in Table 96. However, if the relative risks for ACEi/ARBs were only 1% (men)/1.2% (women) 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.

Table 96: Sensitivity analysis for increased effectiveness of A/B for younger patients (45-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
% improvement in effects of A/B	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
0%	LC	-	-	-	3	£610	-	LC	-	2
1%	-	-	LC	-	1	£5,730	-	LC	-	2
2%	-	-	LC	-	1	-	-	LC	-	1
3%	-	-	LC	-	1	-	-	LC	-	1
4%	-	-	LC	-	1	-	-	LC	-	1
10%	-	-	LC	-	1	-	-	LC	-	1
12%	-	-	LC	-	1	-	-	LC	-	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A dominates all*
2 = B and C dominated: D versus A
3 = D dominates all

Update 2011

I.6.4 Other sensitivity analyses

A range of 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 cost-effectiveness threshold of £20,000 per QALY. Table 97 summarises the results for those parameters that led to a change of conclusion from the base case. These results are discussed further in the sections that follow this table.

Table 97: List of sensitivity analyses results that altered base-case conclusions

Parameters changed	Most cost-effective option
Base case men age 65 (2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)	C
Treatment effects	
Upper limits for effects of C vs D	D
Lower limits for effects of ACEi vs C	A
Lower limits for effects of ARB vs ACEi	A
Alternative treatment effect data scenario 1: lower limits for effects of B vs D	B
Alternative treatment effect data scenario 2: lower limits for effects of ACEi vs D	A
Event risks	
RR of CVD events with diabetes of 4, when risk of diabetes is 4%	A
RR of CVD events with heart failure >11 (base case heart failure risk) and any RR ≥1 when when heart failure risk is 2% and 4%.	D
Quality of life	
Reduction in quality of life from drug side effects 3.6% or more	NI
Reduction in quality of life of 0.27% or more due to side effects of C	D
Costs	
Cost of CCBs more than £94 per annum	D
Highest cost drug in each class used	D

Update 2011

I.6.4.1 Uncertainty over treatment effects

The results are sensitive to uncertainty over the magnitude of treatment effects estimated from the meta-analyses (Table 98, Table 99 and Table 100).

The conclusion that CCBs were the most cost-effective option was robust to variations in the treatment effects, except in the following scenarios:

- 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 three tested scenarios:
  - Lower limits for effects of ACEi versus C (A dominates all interventions).
  - Lower limits for effects of ACEi versus D (£620 per QALY for A versus D).
  - Lower limits for effects of ARB vs ACEi (£840 per QALY for A versus D, C versus A > £20,000 per QALY gained)
- Beta-blockers are the most cost-effective option if we take the lower limits for the effects of B versus D (£2,010 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 98: Sensitivity analysis for efficacy of treatment (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
Comparison	Lower limit of treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C	*
D vs NI	LC	-	-	£970	1	LC	-	-	£4,470	1
C vs D	-	-	LC	£360	2	LC	-	-	-	3
B vs C	LC	-	-	£1,960	1	LC	-	-	£1,960	1
ACEi vs C	-	-	LC	-	4	LC	-	-	£1,960	1
ARB vs ACEi	LC	-	£840	£55,420	5	LC	-	-	£1,960	1

Update 2011

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = Band D dominated: C versus A
3 = D dominates all
4 = A dominates all
5 = B dominated: A versus D, C versus A

Table 99 shows how 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 £2,010.

Table 99: Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (Alternative treatment effect data scenario 1: BB versus DD)

Incremental cost-effectiveness ratios (cost per QALY)															
Comparison	Lower limit of treatment effect					Basecase treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C		D	B	A	C	*
B vs D	LC	£2,010	-	£1,960	1	LC	-	-	£1,960	2	LC	-	-	£1,960	2

Update 2011

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A dominated: C vs D, B versus C*
2 = A and B dominated by C: C versus D

Table 100 shows how 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 base-case 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 100: Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (Alternative treatment effect data scenario 2: ACEi versus DD)

Incremental cost-effectiveness ratios (cost per QALY)														
Comparison	Lower limit of treatment effect					Base-case treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C		D	B	A	C	*
ACEi vs D	LC	-	£620	-	1	LC	-	-	1,760	2	LC	-	-	£1,760	2

Update 2011

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = B and C dominated: A versus D*
2 = A and B dominated: C versus D

I.6.4.2 Use of ARBs

The percentage of ARBs used in conjunction with ACEi in the base-case model was assumed to be 20%. The model is not sensitive to assumptions about the number of patients who cannot tolerate ACEis and switch to ARBs. Varying this percentage up to 100% did not impact conclusions; CCBs remained cost effective (Table 101).

Table 101: Sensitivity analysis, percentage of ARBs used in conjunction with ACEi (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)								
% of ARBs	MEN				WOMEN			
	D	B	A	C	D	B	A	C
0%	LC	-	-	£1,960	LC	-	-	£1,520
10%	LC	-	-	£1,960	LC	-	-	£1,520
15%	LC	-	-	£1,960	LC	-	-	£1,520
20%	LC	-	-	£1,960	LC	-	-	£1,520
25%	LC	-	-	£1,960	LC	-	-	£1,520
50%	LC	-	-	£1,960	LC	-	-	£1,520
60%	LC	-	-	£1,960	LC	-	-	£1,520
70%	LC	-	-	£1,960	LC	-	-	£1,520
80%	LC	-	-	£1,960	LC	-	-	£1,520
90%	LC	-	-	£1,960	LC	-	-	£1,520
100%	LC	-	-	£1,960	LC	-	-	£1,520

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Update 2011

I.6.4.3 Event risk assumptions

Risk of CVD events for people with diabetes

In the base-case analysis it is assumed that the relative risk of CVD event for people with diabetes is 2 (that is the risk of CVD events is doubled). At all levels of diabetes risk, CCBs remained the most cost effective option in most scenarios regarding the relative risks of CVD events; even if the relative risk of CVD events with diabetes was set to 1 (that is, no increase in risk of CVD events in people with diabetes). It is more cost-effective to treat with ACEi/ARB at a high level of diabetes risk (4%) if the relative risk of CVD events is also high (RR = 4).

Table 102: Sensitivity analysis for relative risk of CVD events and diabetes (65-year-old men 2% CVD risk, 1.1% diabetes risk)

Incremental cost-effectiveness ratios (cost per QALY)															
RR **	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	*
1	LC	-	-	£3,760	1	-	-	LC	£1,490	2	-	-	LC	£3,360	2
2	LC	-	-	£1,960	1	-	-	LC	£1,690	2	-	-	LC	£8,620	2
4	LC	-	-	£1,640	1	LC	-	£310	£2,510	3	-	-	LC	-	4

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = D and B dominated: C versus A
3 = B dominated: A versus D, C versus A
4 = D, B and C dominated by A
*** Relative risk of CVD events following heart failure compared with CVD event risks for people who have not had a CVD event*

Update 2011

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 (Table 103). 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 (as in the base-case analysis, CCBs are no longer cost-effective compared with diuretics only if the risks of CVD events with heart failure are more than 11 times higher than in the base case.

Table 103: Sensitivity analysis for relative risk and incidence of CVD events following heart failure (65-year-old men 2% CVD risk, 1.1% diabetes risk)

Incremental cost-effectiveness ratios (cost per QALY)															
RR **	Annual risk of heart failure = 1%					Annual risk of heart failure = 2%					Annual risk of heart failure = 4%				
	D	B	A	C	*	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	-	2	LC	-	-	-	2
2	LC	-	-	£2,960	1	LC	-	-	-	2	LC	-	-	-	2
4	LC	-	-	£4,990	1	LC	-	-	-	2	LC	-	-	-	2

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = D dominates all other options
*** Relative risk of CVD events following heart failure compared with CVD event risks for people who have not had a CVD event*

Update 2011

Risk of CVD events for people with stroke

As shown in Table 104, conclusions are not sensitive to the relative risk of CVD events following a stroke; CCB remains the most cost-effective option.

Table 104: Sensitivity analysis for relative risk of CVD events following a stroke (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
RR**	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	£1,520	1
2	LC	-	-	£1,970	1	LC	-	-	£1,580	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
*** Relative risk of CVD event following stroke compared with CVD event risks for people who have not had a CVD event*

Update 2011

Risk of non-CVD death

As shown in Table 105, conclusions 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 105: Sensitivity analysis for relative risk of non-CVD death (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
RR**	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	£1,520	1

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)										
2	LC	-	-	£1,500	1	LC	-	-	£1,310	1
4	LC	-	-	£1,250	1	LC	-	-	£1,160	1
8	LC	-	-	£1,030	2	LC	-	-	£1,000	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 =A and B dominated: C versus D*
2= A and B dominated: C versus D and D versus NI
*** Relative risk of non-CVD death for population in model (people with hypertension) compared to general population*

I.6.4.4 Quality of life

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 3.6% 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 106: Sensitivity analysis for quality of life loss from hypertensive treatment (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
QoL reduction	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
0%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
1%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
2%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
3%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
4%	LC	-	-	£1,960	2	LC	-	-	£1,520	2
5%	LC	-	-	-	3	LC	-	-	£1,520	2

LC = lowest cost; QoL = quality of life; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = A and B dominated by NI: NI versus C (NI ICER not shown – NI cost effective)
3 = A, B and C dominated by NI: NI versus D (NI ICER not shown – NI cost effective)

Update 2011

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 0.27% (Table 107). 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.

Table 107: Sensitivity analysis for quality of life with CCBs and ACEi/ARBs (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)																
Reduction with C	0% reduction with A				0.2% reduction with A				0.4% reduction with A				0.6% reduction with A			
	D	A	C	*	D	A	C	*	D	A	C		D	A	C	*
0.1%	LC	-	£2,940	1	LC	-	£2,940	1	LC	-	£2,940	1	LC	-	£2,940	1
0.2%	LC	-	£5,890	1	LC	-	£5,890	1	LC	-	£5,890	1	LC	-	£5,890	1
0.4%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)																
0.8%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2
1.0%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2
2.0%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = B and A dominated: C versus D*
2 = D dominated all

Quality of life due to events

Table 108 interpretation: The results are not sensitive to changes in the assumed quality of life change due to CVD events or the onset of diabetes. C remained the most cost-effective option under all scenarios tested.

Table 108: Sensitivity analysis for quality of life loss from CVD events and diabetes (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)										
	Lower limit					Upper limit				
Quality of life loss	D	B	A	C	*	D	B	A	C	*
Unstable angina (0.7-0.9)	LC	-	-	£1,960	1	LC	-	-	£1,950	1
MI (0.7-0.9)	LC	-	-	£1,960	1	LC	-	-	£1,950	1
Diabetes (0.8-1)	LC	-	-	£1,930	1	LC	-	-	£1,990	1
Stroke (0.5-0.7)	LC	-	-	£1,930	1	LC	-	-	£1,960	1
Heart failure (0.6-0.8)	LC	-	-	£2,010	1	LC	-	-	£1,920	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*

I.6.4.5 Costs

Drug costs

In the base-case model, CCBs were assumed to cost £18.64 per patient per annum (based on the BNF 60, September 2010, price of amlodipine). If this is increased to £94 or more, then CCBs were no longer cost effective compared with diuretics.

As shown in table Table 109, the model is sensitive to assumptions about the cost of drugs. CCBs remained the most cost-effective option when the cheapest drugs are used. When the most expensive drugs are used, the ICERs increase to a level above what is usually considered affordable by the NHS, between £20,000–£30,000 per QALY, making D the optimal choice. However, this is an unlikely scenario.

Table 109: Sensitivity analysis for cost of drugs (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (cheapest and most expensive)

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)										
Cost of drugs	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
Cheapest	LC	-	-	£1,960	1	LC	-	-	£1,520	2
Most expensive	LC	-	-	£85,160	1	LC	-	-	£95,660	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*

2 = B dominated: C versus A

As shown in Table 110, the conclusion that CCBs are the most cost effective option is not sensitive to the cost of the diuretics used in the analysis. When chlortalidone is used for costing purposes diuretics are dominated and A becomes the lowest cost option, but CCBs remain the most cost-effective option.

Table 110: Sensitivity analysis on the cost of diuretics (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)								
Thiazide-type diuretic	MEN				WOMEN			
	D	B	A	C	D	B	A	C
Chlortalidone	-	-	LC	£310	-	-	-	LC
Indapamide	LC	-	-	£1,040	LC	-	-	£480

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

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Health state costs

As shown in Table 111, 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.

Table 111: Sensitivity analysis for costs of events (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)								
	Lower limit of costs (50% reduction)				Upper limit of costs (50% reduction)			
	D	B	A	C	D	B	A	C
No event	LC	-	-	£1,940	LC	-	-	£2,000
Unstable angina	LC	-	-	£1,890	LC	-	-	£2,090
Unstable angina sub.	LC	-	-	£1,920	LC	-	-	£2,030
MI	LC	-	-	£1,740	LC	-	-	£2,400
Post-MI	LC	-	-	£1,870	LC	-	-	£2,140
Diabetes	LC	-	-	£2,040	LC	-	-	£1,800
Stroke	LC	-	-	£2,440	LC	-	-	£1,010
Post-stroke	LC	-	-	£1,980	LC	-	-	£1,910
Heart failure	LC	-	-	£1,090	LC	-	-	£3,690
Post heart failure	LC	-	-	£1,260	LC	-	-	£3,370

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Update 2011

I.7 Impact of the 2011 update

I.7.1 Model inputs

The most significant change in the model inputs in the 2011 update was the reduction in drugs costs; in particular the cost of CCBs, ACEis and ARBs.

I.7.2 Base case results

CCBs remained the most cost effective option in the updated base-case analysis, meaning no change from 2006 in the interpretation in terms of overall cost effectiveness. The ICER for CCBs did however reduce considerably (from £12,250 to £1,960) making CCBs more cost effective than they were in 2006.

Due to reductions in drug costs since 2006 overall costs for all drug classes in the updated analysis were cost saving compared with no intervention (based on low cost generic options); in 2006 this was only the case for diuretics. As cost reductions for drugs were relatively greater for CCBs, ACEis and ARBs than other classes CCBs were also no longer the most expensive option, both B and NI being more expensive. In addition the overall costs of the ACEi/ARB or CCBs options were much similar to those for diuretics in the updated analysis; in the 2006 analysis ACEi/ARB and CCBs had considerably higher costs than diuretics.

I.7.3 Subgroup and sensitivity analysis results

The results of the subgroup analysis (by age, annual CVD, diabetes and heart failure risk) remain largely unchanged although, in both men and women, CCBs are the most cost effective option in a greater number of scenarios; however, this difference is not great. Both old and new analyses show similar trends of cost effectiveness but in the new analysis A is the most cost effective option in fewer scenarios than before with the heart failure risk where this is the case moving to intermediate/high risk.

Table 112 summarises how the other sensitivity analysis results have changed in the 2011 update from the 2006 analysis.

Table 112: Changes to the interpretation of sensitivity analyses from 2006 update

Sensitivity analysis	Interpretation changes
Younger people	**No change.**
Treatment effects	**Minor changes:** C cost effective in women with upper limits of B vs C – differs from 2006 where A is the cost effective option and C is dominated.
Use of ARBs	**Minor changes:** conclusion nolonger sensitive to this input.
Relative risk of CVD events with diabetes	**Minor changes:** C now remains cost effective even when no increase in risk of CVD events for people with diabetes (RR = 1).
Relative risk of CVD events following heart failure	**Minor changes:** C remains cost effective to a higher increase in risk of CVD event for people with heart failure.
Relative risk of CVD events following a stroke	**No change.**
Non-CVD death	**No change.**
Quality of life loss from hypertensive treatment	**No change.**
Quality of life loss with CCBs and ACE/ARBs	**Minor changes:** quality of life loss required for C to nolonger be cost effective has increased slightly.
Quality of life loss from CVD events and diabetes	**No change.**
Cost of drugs	**No change.**
Cost of diuretics	**New analysis:** no change in base case interpretation.
Costs of events	**No change.**

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I.8 Limitations of the model

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

Firstly, it was 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 CCBs versus diuretics increases to about £2000 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.

Secondly, the data for diuretics in the model was based on the meta-analysis undertaken for the 2006 pharmacological update (CG34) that pooled data for thiazide and thiazide-like diuretics together (referred to collectively as thiazide-type diuretics). The 2011 update reviewed the evidence for the different types of diuretics and concluded that there was limited data for thiazide diuretics at appropriate doses and so recommended that a thiazide-like diuretic (chlortalidone or indapamide) was a more evidenced-based therapy option. However, the data used for diuretic treatment effect in the model was heavily weighted by the very large ALLHAT study which used chlortalidone; therefore it was considered that this was unlikely to significantly impact conclusions.

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A third 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 '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 forth 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-type diuretics is quite sensitive to assumptions about their relative side effects. Further research in this area is likely to be worthwhile.

Fifth, 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 sixth 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 and the other priorities for new analysis it was not possible to conduct a probabilistic sensitivity analysis with the model. This further analysis may be useful, particularly given the sensitivity of the results to extreme assumptions about the relative treatment effects.

I.9 Conclusions

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This analysis found that treating hypertension is highly cost-effective. Treatment resulted in improved health outcomes (higher QALYs) and with allof the drug classes in the model actually resulted in overall cost savings compared to no treatment as the reduction in cardiovascular events led to savings that offsets the relatively low cost of antihypertensive medication; although it should be noted that this is based on low cost generic drugs. In most people CCBs were found to be the most cost-effective treatment option for initial treatment of essential hypertension.

This analysis suggests that which of the drug classes is most cost-effective depends on their relative effects on the prevention of diabetes and heart failure. The model predicts that for people at low to intermediate 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. Thiazide-type 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, ACEis 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, thiazide-type 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.