National Institute for Health and Care Excellence

Draft for Consultation

Hypertension in adults: diagnosis and management

Appendix 1: Cost-effectiveness analysis: treatment initiation threshold for people with stage 1 hypertension

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Economic analysis report

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1.1 Introduction

One of the key clinical issues explored in the 2019 guideline update was the threshold for initiation of antihypertensive drug treatment in terms of either blood pressure (BP) or cardiovascular (CV) risk.

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

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

The 2011 recommendations for treatment initiation amongst those with stage 1 hypertension incorporate a cardiovascular risk based component, which was based on consensus:

- Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:
  - target organ damage
  - established cardiovascular disease
  - renal disease
  - diabetes
  - a 10-year cardiovascular risk equivalent to 20% or greater. **[new 2011]**

Given the evidence identified for different blood pressure initiation thresholds and the fact that the previous risk-based recommendation was consensus based, the committee agreed that it was a high priority to evaluate at which risk level it is cost effective to initiate antihypertensive drug treatment in people with stage 1 hypertension without target organ damage, established cardiovascular disease (CVD), renal disease or diabetes.

A similar evaluation was recently undertaken as part of the NICE lipids guideline update and so it was agreed that it would be appropriate to take a similar approach for this guideline. [34]

1.2 Methods

1.2.1 Model overview

A cost–utility analysis was undertaken where lifetime quality-adjusted life-years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance.[37] An incremental analysis was undertaken.

1.2.1.1 Comparators

The comparators in the analysis were:

- Antihypertensive drug treatment

- No antihypertensive drug treatment

The comparators were compared in the following 10-year QRISK2 cardiovascular risk subgroups to assess whether it is cost effective to use antihypertensive drug treatment in each risk group:

- 5%
- 10%
- 15%
- 20%

Note that QRISK2 was specified as it is recommended by NICE for risk calculation and it was assumed it was most likely to be used to assess risk in practice. However, that risk was pre-defined for the subgroups and was not calculated in the model using the tool. Minimum possible risk levels for particular age and sex groups were, however, calculated using QRISK2 to aid interpretation of the results (this is discussed in section 1.2.4.1).

1.2.1.2 Population

The population considered in the analysis was adults with primary stage 1 hypertension (BP 135/85mmHg and above and below 150/95 mmHg on ambulatory blood pressure monitoring [ABPM]), who do not have target organ damage, established CVD, renal disease or diabetes.

In the base-case analysis, the model was run using a starting age of 60 for both men and women. This was considered to be a typical age at diagnosis of stage 1 hypertension (as identified from analysis of the Health Survey for England 2006,[43] for those with untreated stage 1 hypertension between the ages of 35–80). Alternative starting ages (age 40, 50, 60, 70, and 75) were analysed in sensitivity analyses within each risk subgroup and by sex.

An analysis was not run for people under 40. Hypertension is less frequent in people under 40, and the committee highlighted that there are other considerations when deciding about initiating treatment, such as the abnormal nature of this occurring, often related to secondary causes or strong family histories of premature hypertension and it was felt to more likely require treatment on an individual basis.

An analysis was not run for a starting age of 80 because this population was not included as part of the recommendation relating to this model, as there are also other considerations when initiating treatment in people over 80, such as their inherent higher risk, frailty and other comorbidities. A separate consensus based recommendation was made for this group considering these factors.

The QRISK2 calculator, like all cardiovascular risk calculators, is strongly dependent on age and sex, which account for most of the attributable risk within any estimate. As a result, the vast majority of people aged under 40 years will have a 10-year risk <5% for cardiovascular events, while those aged >80 years will all have a calculated 10-year risk that exceeds 20%. Therefore, those under 40 and over 80 would not fit into the risk subgroups being modelled.

1.2.2 Approach to modelling

The benefit of antihypertensive treatment is that it reduces the risk of having a cardiovascular event. Therefore, in order to reflect differences between initiating drug treatment and not initiating drug treatment, the model includes death due to any cardiovascular cause (CV death) and 6 non-fatal CV events: stable angina (SA); unstable angina (UA); myocardial infarction (MI); transient ischaemic attack (TIA); stroke; and heart failure (HF). Non-CV death is also incorporated although this should not be significantly impacted by antihypertensive drug treatment.

Note that definitions of CVD vary. The events included in the model were agreed with the committee. The QRISK2 definition of cardiovascular disease includes TIA, stroke (ischaemic and haemorrhagic), unstable angina, stable angina, and MI. The committee agreed that it was important to include heart failure in the model, as there is evidence that antihypertensive treatment reduces the risk of heart failure.

In reality, it is plausible that there may be other cardiovascular events that could be impacted by taking antihypertensive drug treatment that haven't been included in this model such as peripheral arterial disease (PAD). In addition, there may be other benefits to taking antihypertensive treatment such as reduced renal impairment from progressive hypertensive nephropathy and reduced retinopathy, arterial aneurysms and dissections, which are not modelled. The committee agreed that omitting these potential effects was a reasonable approach because it would affect both those modelled to receive treatment and those modelled not to receive treatment at any given threshold; however, it could mean the estimates of benefit from treatment are conservative, thus the beneficial effects of treatment may be greater than those the model predicted.

1.2.2.1 Model structure

A Markov model was constructed to calculate lifetime costs and QALYs for each comparator.

In a Markov model, a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

Figure 1 illustrates the health states in the model and transitions between them in each cycle. A 1-year cycle length was used. All people entered the model in the 'No CVD event' state.

For each non-fatal CV event, 2 health states were used in the model: an 'event' state (for example, MI), and a 'post-event' state (for example, post-MI). This is so that a different cost can be applied in the first cycle reflecting acute management and/or diagnostic costs, and so that different quality of life values can be applied for the acute state and for the post-event states. The event state is a tunnel state where people move automatically to the post-event state in the next cycle (unless they die).

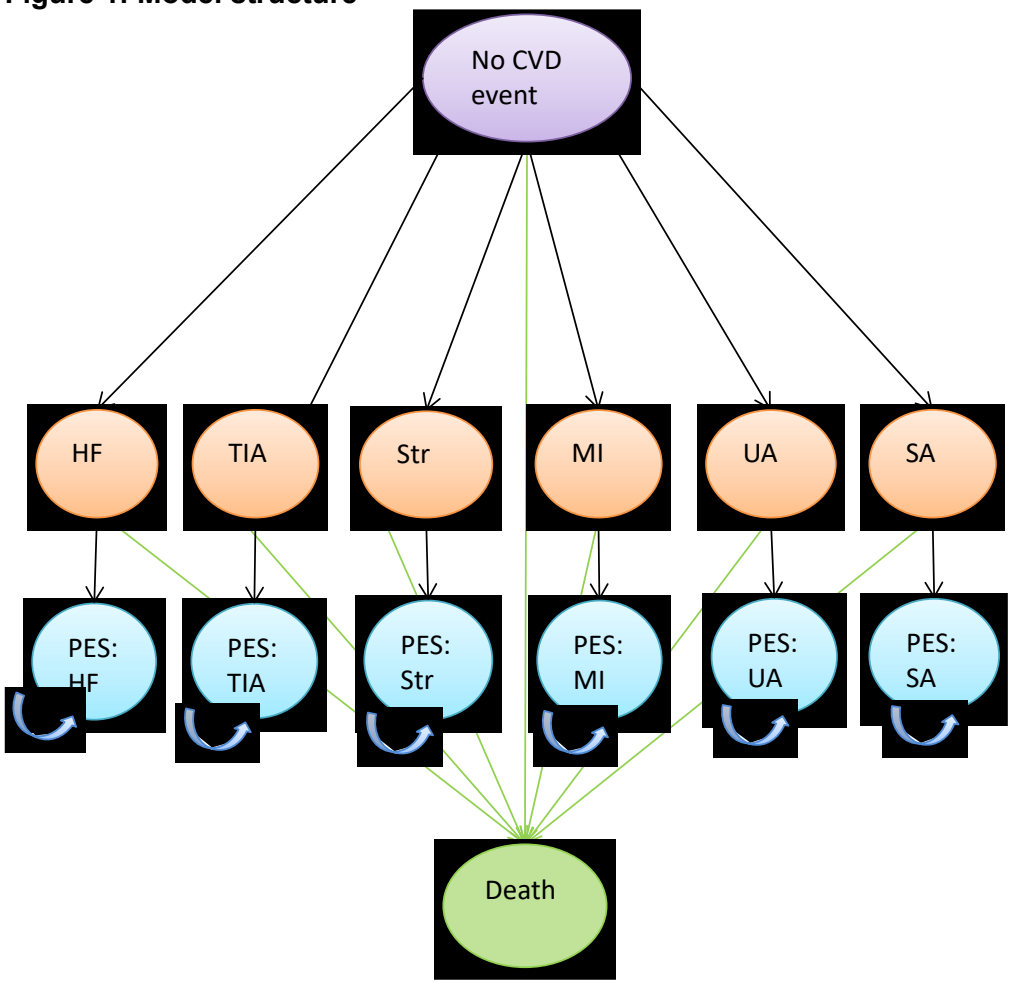
In the model, it was assumed that once a person has moved to a non-fatal event state (SA, UA, MI, TIA, stroke, or HF), they stay there unless they die: that is, repeat events were not explicitly modelled. This was considered a reasonable simplification for modelling purposes and reflects what happens in many trials where an individual is censured at their first event. It is acknowledged that people who have one vascular event through inadequately treated hypertension often go on to have another. Therefore, by avoiding the first event through treatment, a sequence of events could have been avoided rather than only the first. The model results are therefore likely to be a conservative estimate of the cost-effectiveness of treatment.

The probability of death was increased in the CVD states and varied by type of event. Once people moved to the dead state in the model, they could not move elsewhere; this is known as an absorbing state. If the model is run long enough, everyone will eventually be in this state. This model was run for 60 cycles (60 years) by which time most people in the model will have died as people entering the model had a minimum age of 40 years.

The model structure was the same for the antihypertensive drug treatment and no antihypertensive drug treatment arms; however, transition probabilities varied due to CV risk reduction with treatment. This resulted in different total costs and QALYs with each

comparator. Comparing these results allowed us to identify whether treatment or no treatment was the most cost-effective.

Figure 1: Model structure



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

1.2.2.2 Differential treatment duration

In the model, people in the 'no treatment' group did not receive antihypertensive drug treatment for the rest of their lives unless they had a cardiovascular event.

This is a simplification of reality because the decision about whether to initiate treatment is not a one-off decision that is implemented for the whole of the person's lifetime. People should be reviewed annually if they have been diagnosed as having stage 1 hypertension but do not meet the criteria for drug treatment, as recommended in the previous guideline. Any of the following would lead to people starting antihypertensive treatment: blood pressure increasing (to stage 2 hypertension); CV risk increasing (to over 20% based on current recommendation); developing target organ damage; established CVD; or developing other comorbidities, such as diabetes. Note that the model already took into account people going onto treatment following a CV event.

The committee, however, agreed that this approach was reasonable for modelling purposes given the complexity of modelling such changes over time. This approach was also taken in the modelling undertaken for the NICE Lipids guideline.[34] However, not considering that people may become eligible for treatment at some point in the future because of other reasons (other than having a CV event) may also overestimate treatment benefit. To address

this limitation, we undertook sensitivity analyses to explore shorter differential treatment durations. That is, while in the base–case people in the no treatment group never received treatment (unless they experience a CV event), in a sensitivity analysis we explored them starting treatment after a defined time period (for example, 5 years). This meant that treatment varied between groups only in the first 5 years, after which both groups accrued the benefits and costs of treatment. It should be noted that it was still important to undertake a lifetime analysis because costs and QALYs will continue to vary between groups over time because there will be differences in the number of people alive and the distribution of CV health states between the treatment and no treatment groups.

This analysis addressed whether treating for shorter durations, because people may become eligible for treatment due to other reasons in the future, was cost-effective, and at what risk level. As there is uncertainty regarding when people might develop other indications for treatments, different time periods were assumed in the model and their respective impact on the overall results analysed.

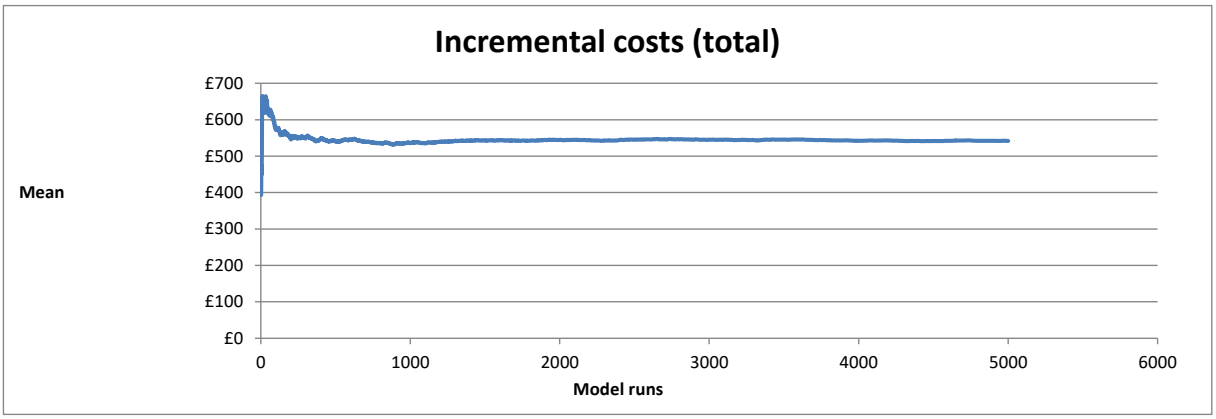
Note that we considered if it would be more appropriate to more explicitly model transitions to treatment in the no treatment arm. We considered various options including a population-based model where CV risk and underlying BP were modelled over time, so that when people might begin treatment in the no treatment arm could be explicitly considered. It was, however, considered unfeasible to capture all these factors appropriately. It was agreed that the approach described above where shorter differential treatment durations were explored was sufficient to address this consideration.

1.2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution and average costs and QALYs per person were calculated using these values. The model was run repeatedly – 5,000 times for the base case and each probabilistic sensitivity analysis – and the results were summarised in terms of mean costs and QALYs, and the percentage of time treatment was the most cost-effective strategy at thresholds of either £20,000 or £30,000 per QALY gained.

When running the probabilistic analysis, multiple runs were required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis, we checked for convergence in the incremental costs and QALYs at a threshold of £20,000 per QALY gained for drug treatment versus no drug treatment by plotting the number of runs against the mean outcome at that point (see example in Figure 2) for the base-case analysis. Convergence was assessed visually. All had converged before 5,000 runs, but 5000 runs was used to ensure convergence and similarity between deterministic and probabilistic sensitivity analysis results.

Figure 2: Convergence graph example



The way in which distributions were defined reflects the nature of the data, so for example probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that probabilities will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1 and in the relevant input summary tables in section 1.2.3. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Distribution of first events. Distribution of people on 1, 2 and 3 drugs	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of people in the sample and the number of people in a particular subgroup.
Heart failure incidence	Beta	Bounded between 0 and 1. Derived from mean and its standard error using the method of moments. Alpha and beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ $\text{Beta} = \text{alpha} \times [(1-\text{mean})/\text{mean}]$
SMRs Relative risks	Lognormal	The natural log of the mean was calculated as follows: $\text{Mean} = \ln(\text{mean}) - \text{SE}^2/2$ An adjustment was made to the ln (mean) of subtracting half the variance, so that the mean of the simulated relative risks is equal to the mean point estimate.[3] Where the natural log of the standard error was calculated by: SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$

Parameter	Type of distribution	Properties of distribution
Probability of adverse events	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: Alpha = (number of people having event) Beta = (Number of people) − (number of people having event)
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and beta values were calculated as follows: $Alpha = mean^2 \times [(1-mean)/SE^2] - mean$ $Beta = alpha \times [(1-mean)/mean]$

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- the cardiovascular risk levels or increase in risk (as these would vary from their predefined values if they were to be made probabilistic),
- the resource, including time and cost of staff, required to implement each strategy (assumed to be fixed according to national pay scales and programme content),
- health state costs (based on other guidelines or sources that already use national average costs from UK national sources),
- utility decrements (the standard error around the utility loss from a fall was not reported in the source to allow appropriate parameterisation. However, the probabilities of adverse events were probabilistic, which would impact the QALY loss and the impact of adverse events was further tested in deterministic sensitivity analyses).
- The length of stay following a fall (the standard error around the input was not reported in the source to allow appropriate parameterisation. However this was subject to deterministic sensitivity analysis using alternative values)

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis was rerun to evaluate the impact on results. Details of the sensitivity analyses undertaken can be found in methods section 1.2.4 Sensitivity analyses.

1.2.3 Model inputs

1.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Summary of base-case model inputs

Input	Data	Source
Comparators	No antihypertensive drug treatment Antihypertensive drug treatment	

Input	Data	Source
Population	People with stage 1 hypertension.	
Subgroups	10 year QRISK2 cardiovascular risk: • 5% • 10% • 15% • 20% Sex: • Male • Female	
Age (entering model)	60 years	
Perspective	UK NHS and PSS	NICE reference case.[37]
Time horizon	Lifetime	NICE reference case.[37]
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case.[37]
Baseline risk		
10 year CV risk (SA, UA, MI, Stroke, TIA, CV death)	As defined per subgroup	
Distribution of first CV events across QRISK2 events (SA, UA, MI, Stroke, TIA, CV death)	3.4%-46.4% Event, age group, and sex dependent	Ward 2005.[39]
Heart failure risk	6.3%-26.1% Age group and sex dependent	Cowie 1999.[10]
Annual increase in risk for CHD (coronary heart disease) (SA, UA, MI, CHD death)	Men: 0.03% Women: 0.008%	Ward 2005.[39]
Annual increase in risk for TIA, stroke, heart failure	Assumed to increase based on frequency of events relative to CHD events	Assumption
Non-CV mortality	Age and sex dependent	ONS life tables for England, 2014-16.[41] Proportion of deaths that are non-circulatory based on ONS.
Stable angina SMR	1.95 (1.65-2.31)	Rosengren 1998.[46]
Unstable angina SMR	2.19 (2.05-2.33)	UA/NSTEMI NICE guideline.[28]
MI SMR	2.68 (2.48-2.91)	Bronnum-Hansen 2001.[7]
TIA SMR	1.4 (1.1-1.8)	Dennis 1990. Oxfordshire Community Stroke Project.[15]
Stroke SMR	2.72 (2.59-2.85)	Bronnum-Hansen 2001.[6]
HF SMR	2.20 (1.98-2.42)	Chronic heart failure natriuretic peptides decision thresholds model. [38]
Treatment effect		
Relative risk of CHD event (SA, UA, MI)	0.84-0.91 (age and sex dependent)	Guideline clinical review (based on Brunström 2018).[8] Age adjustments made using Law 2009.[23]

Input	Data	Source
Relative risk of stroke/TIA event	0.81-0.93 (age and sex dependent)	Guideline clinical review (based on Brunström 2018).[8] Age adjustments made using Law 2009. [23]
Relative risk of HF event	0.82-0.94 (age and sex dependent)	Guideline clinical review (based on Brunström 2018).[8] Age adjustments made using Law 2009. [23]
Relative risk of CV death	0.81-0.92 (age and sex dependent)	Guideline clinical review (based on Brunström 2018).[8] Age adjustments made using Law 2009. [23]
Adverse events		
Annual probability of acute kidney injury (AKI; that led to hospitalisation)	0.003	Guideline clinical review for targets (SPRINT trial).[52]
Annual probability of a fall (injurious fall that led to hospitalisation)	0.008	Guideline clinical review for targets (SPRINT trial).[52]
Over 75s AKI relative risk	2.29	SPRINT (sub study on AKI). [45]
Costs – drugs and monitoring (d)		
Drug costs	£19.66- £24.79 (age group and sex dependent)	Drug costs from the British National Formulary (BNF).[19] Weighted averages based on distribution of number of drugs (based on Clinical Practice Research Datalink [CPRD] data from GC member contact), and class of drug.
Monitoring costs – first year (on treatment)	£118 - £129 (Age group and sex dependent)	Resource use: guideline committee Costs: PSSRU 2017, [12] NHS reference costs 2016-17,[17] NICE CKD guideline.[33]
Monitoring costs – subsequent years (on treatment)	£76	No. of GP consultations based on CPRD data[26]. Other resource use from guideline committee. Costs: PSSRU 2017,[12] NHS reference costs 2016-17,[17] NICE CKD guideline.[33]
Monitoring costs (no treatment), all years	£38	GP consultation, PSSRU 2017.[12]
Costs – Cardiovascular events and adverse events		
Stroke	£23,076	Xu et al 2016 - SSNAP project.[47]
Post stroke	£5,183	Xu et al 2016 - SSNAP project.[47]
TIA	£1,746	Danese 2016. [13]
Post-TIA	£587	Danese 2016. [13]
MI	£4,641	Danese 2016. [13]
Post-MI	£768	Danese 2016. [13]
SA	£908	NHS reference costs 2016-17.[17]
Post-SA	£273	Assumed same as post stable angina
UA	£2,336	Danese 2016. [13]

Input	Data	Source
Post-UA	£273	Danese 2016. [13]
HF	£2,719	Danese 2016. [13]
Post-HF	£706	Danese 2016. [13]
Cost of fall	£2,378	Resource use taken from Falls: assessment and prevention of falls in older people NICE guideline.[36] Length of stay from Kenny et al 2002.[20] Cost associated with resource use and cost per day from NHS reference costs 2016-17.[17]
Cost of AKI	£1,941	NHS reference costs 2016-17.[17]
Utilities (age and gender dependent) (a)		
General population utility	0.759-0.895 (Age group an sex dependent)	Health Survey for England 2014.[42]
Utility multipliers (b)		
Well	1	By definition
SA	0.808	Melsop 2003.[27]
Post-SA	0.808	Melsop 2003.[27]
UA	0.770	Goodacre 2004,[18] Ward 2005 [39]
Post-UA	0.880	2008 Lipid modification guideline.[35]
MI	0.760	Goodacre 2004,[18] Ward 2005 [39]
Post-MI	0.880	Tsevat 1993.[51]
TIA	0.900	Lavender 1998.[21]
Post-TIA	0.900	Lavender 1998.[21]
Stroke	0.628	Tengs 2003,[50] Youman 2003[54]
Post-stroke	0.628	Tengs 2003,[50] Youman 2003[54]
HF	0.683	Davies 2006.[14]
Post-HF	0.683	Davies 2006.[14]
CV death, Non-CV death	0	By definition
Utility decrements (c)		
Fall utility decrement	-0.343	Peasgood 2009.[44] Utility decrement applied for 4 weeks.
AKI utility decrement	-0.323	NICE AKI guideline.[32] Utility decrement applied for 4 weeks.

Abbreviations: AKI: acute kidney injury; CV: cardiovascular; HF: heart failure; MI: myocardial infarction; SMR: standardised mortality ratio; SA: stable angina; TIA: transient ischaemic attack; UA: unstable angina

(a) These are applied to the model population and represent baseline quality of life associated with age and gender.

(b) These are utility multipliers. When a person has an event in the model then their age and gender related quality of life is adjusted by being multiplied by the multiplier associated with the particular event.

(c) These are utility decrements and are multiplied by the duration they apply for to create a QALY loss associated with having the adverse event, and this QALY loss is subtracted from the total QALYs a person has accrued in the model.

(d) Note the versions of NHS cost sources (of PSSRU and NHS reference costs) used were the latest ones at the time of model construction.

1.2.3.2 Initial cohort settings

The base case was run for a cohort aged 60, both male and female, for all CV risk subgroups (5%, 10%, 15%, and 20%).

1.2.3.3 Transition probabilities with no treatment (baseline risks)

As described in Section 1.2.2.1 above, possible transitions were defined between each of the health states in the model and the probability of each transition occurring within a defined period (a cycle; a year in this model) was assigned to each possible transition.

This section describes sources and calculations for transition probabilities without treatment (also referred to as baseline risks):

1. CV events (fatal and non-fatal)
2. Non-CV mortality
3. Mortality post-CV events

1.2.3.3.1 CV events

Each cycle (each year), people in the 'no CV event' state in the model could transition to the various different CV event health states of CV death, and non-fatal stroke, TIA, MI, UA, SA, and HF.

Annual transition probabilities were calculated for each CV event in the model following the methodology used in the Lipids guideline model,[34] taking into account:

- The QRISK2 10-year CV risk of the subgroup being analysed (5%, 10%, 15% or 20%)
- Information about the relative distribution of the different types of CV event that make up this risk, and information about CV events not included in QRISK (heart failure)
- How CV risk changes over time.

Transition probabilities therefore changed over time for each subgroup being analysed because of two reasons: firstly, within the overall risk of any CV event, the breakdown of which event is more or less likely varied with age and sex (for example, the probability of heart failure increases with age, but the risk of stable angina decreases with age). Secondly, the overall risk of any CV event increased with each cycle as the cohort aged, as age is the main determinant of risk.

The formula below summarises how transition probabilities were calculated. The details are discussed in turn in the sections below.

Equation 1: Calculation for transition probabilities

		CV event-specific risk				**CV event-specific time adjustment**			
Annual transition probability for CV event X in cycle Y	=	Average annual CV risk[(a)]	x	Relative distribution % for CV event X[(b)]	+	(Annual increase in risk for CV event X[(c)]	x	Time adjustment [Cycle Y - 5.5]	)

(a) The analysis is run for different 10-year QRISK2 defined subgroups: 5%, 10%, 15%, and 20%. See Model Overview for more information,
(b) Varies by age and sex
(c) Varies by sex

In brief: The QRISK2 CV risk is a 10-year predicted risk, and this is annualised in the model (average annual CV risk) and spread over the CV events in the model by being multiplied by the distribution of events. As the model also included an annual increase in risk over time, then time adjustment was necessary because the average annual CV risk was applied in such a way that the risk in the first year started below the average annual CV risk and ended up higher than the average annual CV risk at the end of the 10-year period. So, the risk compounded over the first 10 years is equal to the annualised 10-year risk and includes the risk increasing over time.

The specific components forming the transition probabilities are discussed in more detail below.

Calculating the CV event-specific risk element

The risk of a first cardiovascular event in the model was made up of 2 components:

1. CV risk – as defined for the CV risk subgroup for example, 10% 10-year risk of CVD event (SA, UA, MI, TIA, stroke, CV death).
2. the relative distribution of each type of CVD event (SA, UA, MI, TIA, stroke, CV death) and heart failure – which varied by age and sex.

These are explained further below.

1. The initial overall risk of cardiovascular events without treatment was part of the definition of each subgroup, for example 10% 10-year risk. This 10-year risk was converted to an average annual CV risk by first converting the 10-year risk to a rate and then converting this to a 1-year probability, using the following formulae:

Equation 2: Formulae for converting 10-year risk to a 1-year probability

$Selected\ rate\ (r) = -\ln(1-P)/t$	Where P = probability of event over time (t) t = time over which probability occurs (10 years)
$Transition\ probability\ (P) = 1-e^{-rt}$	Where r = selected rate t = cycle length (1 year)

2. The risk subgroups were defined by QRISK2, as this is what would be used in practice. The relative distribution of first CV events that are included in the QRISK2 tool (SA, UA, MI, TIA, stroke, CV death), were based on the same source as the NICE Lipids and Hypertension guideline models: Ward 2005.[39] These can be seen in Table 3**.**

Heart failure is not included in the QRISK2 tool but was included in the model. Therefore, the relative distribution for heart failure was calculated using the incidence of heart failure relative to the total incidence of the other CV events. The incidence of heart failure was also taken from the Lipids model (Cowie 1999[10]). This means that as the total incidence of the events included in the QRISK2 tool changes, the distribution of heart failure events also changed in a proportional way. This is why the sum of the relative distribution of the events included in QRISK2 summed to 100% (Table 3), but adding the relative distribution of heart failure made this sum to more than 100% because heart failure is an additional event outside of the QRISK2 tool. It is important to remember that the definitions of the CV risk subgroups in this model were referring to CV risk from the QRISK2 tool. Heart failure is not included as part of that risk but as antihypertensive treatment reduces the incidence of heart failure, this should

be interpreted as drug treatment having a greater benefit than suggested by prescription based on QRISK2 risk levels. In other words, decisions in practice are based on the risk output of the QRISK2 tool, but the drug treatment itself may have a wider benefit, which has been captured by the results of this model in terms of the costs and QALYs. The relative distributions of events including heart failure can be seen in Table 3.

Table 3: Relative distribution of CV events including heart failure

Age	SA	UA	MI	TIA	Stroke	HF	CVD death	Total CVD risk relative to QRISK2 defined risk (b)
Male								
40-44	30.7%	10.7%	29.5%	6.0%	12.9%	7.1%	10.1%	107.1%
45-54	30.7%	10.7%	29.5%	6.0%	12.9%	7.1%	10.1%	107.1%
55-64	32.8%	7.1%	17.2%	8.9%	20.6%	12.4%	13.4%	112.4%
65-74	21.4%	8.3%	17.3%	10.0%	27.0%	16.0%	16.0%	116.0%
75-84	19.1%	8.1%	16.1%	8.0%	34.3%	26.1%	14.3%	126.1%
Female								
40-44	32.4%	11.7%	8.0%	16.0%	22.9%	6.3%	9.1%	106.3%
45-54	32.4%	11.7%	8.0%	16.0%	22.9%	6.3%	9.1%	106.3%
55-64	34.6%	7.3%	9.2%	9.5%	28.8%	10.6%	10.6%	110.6%
65-74	20.2%	5.2%	12.1%	7.3%	38.2%	18.5%	17.1%	118.5%
75-84	14.9%	3.4%	10.2%	9.8%	46.4%	25.2%	15.2%	125.2%

(a) There was no data for age below 45 and so the age 40 subgroup (35-44 age range) data is the same as the age 50 subgroup data (45-54 age range).

(b) The total CVD risk sums the distribution of all columns (that is, events) in the table, so this also includes heart failure, which is not included in QRISK2.

The CV event specific risk of first events were based on the above distributions multiplied by the annual CV risk being modelled, that is for the QRISK2 10% subgroup, the transition probabilities were the 10% 10-year risk turned into an annual risk, which was then apportioned according to the distributions in Table 3.

It is important to make clear that in the model, cardiovascular risk was determined only by the pre-defined risk subgroup. In particular, the starting age of the model was not influencing risk. For example, if the focus was on the 10% risk subgroup: whether the starting cohort was aged 40 or 70 did not affect the level of risk, as the CV risk being modelled is still a risk of 10%. However, the distribution of events within that 10% risk was different for the different age groups.

The reason that age subgroups are incorporated into the model is because a younger cohort will live longer in the model; therefore, an event avoided from a young age would accrue benefits over a longer period of time. Additionally, non-cardiovascular mortality varies by age, and the distribution of events that make up the pre-defined risk levels vary by age as mentioned above.

The distributions of events that make up QRISK2 are from sources based on the late 1980s and 1990s. It was accepted that incidence rates in absolute terms are likely to have changed over time; however, the committee agreed that was less likely to have affected the distribution of events in relation to each other. The British Heart Foundation reports statistics on morbidity and mortality of cardiovascular conditions using a variety of sources. Their 2018 report[5] confirms that the distribution of events relative to each other are approximately correct, for example: CHD is around twice as common as stroke. The report also confirms that the relationship between different types of events for different sexes in the model

seemed to have face validity (such as strokes tend to be more common in women compared to other events like MI).

The distributions of CV events that make up QRISK2 were made probabilistic using the Dirichlet distribution (see Table 1). The total rate of CV events per 100,000 and the deterministic distribution of events were multiplied to derive the raw data for the Dirichlet distribution, as the raw incidences of each event were not available. Although using this method may derive different numbers of events compared to the raw data of each type of event from the original studies, the method described was considered a reasonable approach that was likely to be similar to the original data given the event rates were derived from large registries with cohorts of over 100,000 such as the Oxfordshire community stroke project and the Bromley coronary heart disease register.

The distribution of heart failure events was made probabilistic by making the incidence probabilistic using the beta distribution parameterised using the method of moments approach assuming a standard error of 10% (see Table 1).

Calculating the CV event-specific time adjustment element

The CV event specific time adjustment was made up of 2 components:

1. Annual increase in risk
2. Time adjustment.

These are explained further below.

1. In the model, the annual risk of a first CV event increased by a fixed amount each year to account for increasing risk due to age. The increase in risk was applied as an additive percentage increase in risk per year increase in age. The amount the risk rose was based on Ward 2005,[39] which estimated an approximate linear relationship between increasing age and the risk of angina, MI, or CV death (that is, CHD events) by analysing the Health Survey for England data 1998. Ward et al estimated an annual increase in the risk of experiencing any of these events of 0.03% for men and 0.008% for women.

As these annual increases in risks were in relation to the risk of CHD, then in the model the annual increase in risk was applied to the risk of each first CV event relative to the total risk of all CHD events (stable angina, unstable angina, MI, and deaths that are CHD). The risk of TIA, stroke, and heart failure (which were not factored into the analysis by Ward et al) were also increased each year in the model, in proportion to their relative frequency in relation to the CHD events. For example, if we take a man aged 60, the annual increase in the risk of a stroke would be:

Equation 3: Annual increase in risk example calculation

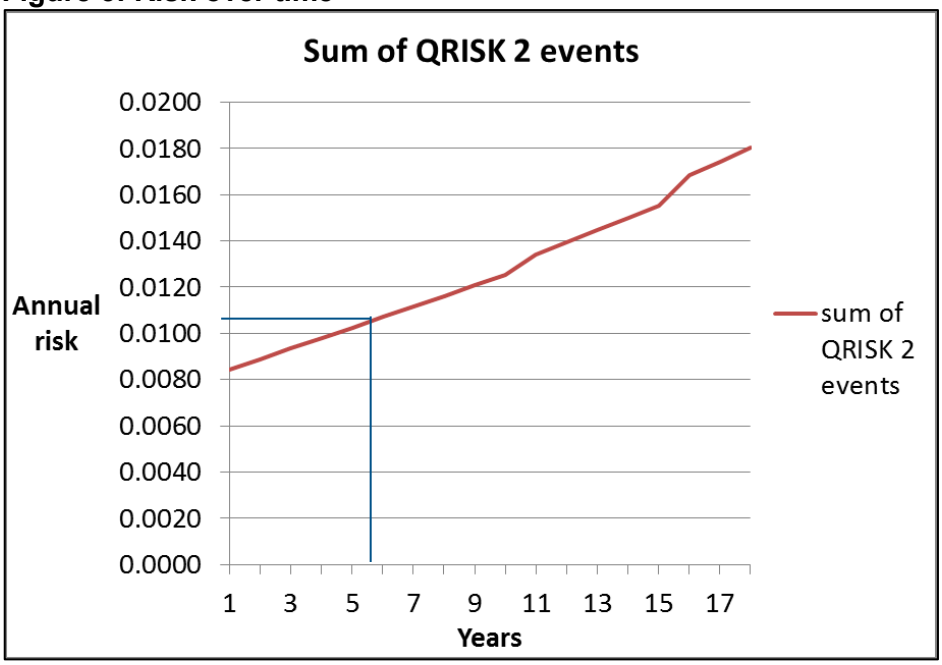
$$\text{Annual increase in risk of a stroke for man aged 60} = \frac{[\text{Risk of stroke for man aged 60}}{\text{total CHD risk for man aged 60 (sum of risks of stable angina, unstable angina, MI, and CHD death)]}} \times \text{Annual increase in risk for males of 0.03\%}$$

2. In terms of how the transition probabilities were applied in the model, the CV event specific risks of each first event were set below the average annual CV risk in the first year, so as age-related risk increased, the total risk was equal to the average annual CV risk in the middle of the first 10-year period (which would be at 5.5 years, as people entered the model in cycle 0; cycles 0 to 10 equates to 11 cycles inclusively), and above the average annual CV risk by the end of the 10-year period. This meant that the total risk compounded over 10 years including both average annual CV risk and age-related risk

was exactly equal to the predicted 10-year risk. This is effectively the application of the formula summarised in Equation 1. Since annual risk continued to increase each year with age, it was noted that the risk following the 10-year period continued to rise.

For example, see the graph below that describes males aged 60 who are in the 10% risk subgroup. A risk of 10% is equivalent to an annual risk of 1.05%. As can be seen from the graph, the total risk is equal to the baseline annual risk at 5.5 years, as explained above. The risk then continued to increase beyond 10 years (note there are kinks at certain years because of how the distribution of events changes when people reach certain ages, for example a person entered the model aged 60 then survived until age 70 and 75, which are specific age subgroups in the model and points at which the distribution of events could change).

Figure 3: Risk over time



Note that the slope does not appear straight because of how the risk of events change as an individual ages as different age subgroups have a different distributions of events.

The annual increase in risk was not made probabilistic in the model, but the annual increase in risk for females was subject to sensitivity analysis, as the committee felt this might be being underestimated. See sections 1.2.4.9 and 1.2.4.10.

Adjusting annual CV risk increase at very low levels of QRISK risk

At very low levels of 10-year risk (below 1.34% for men and below 0.36% for women), the model predicted negative probabilities of CV events. This is because of the time adjustment method used to attribute the annual baseline risk in the middle of the 10-year period as described above. This meant that the risk in the first year started below the annual baseline risk, and was higher than the annual baseline risk at the end of the 10 years. Hence, at very low levels of annual baseline risk, the risk in the beginning of the 10-year period could be below 0. See Figure 4 for an example for a risk of 0.5% for 60-year-old men leading to risks below zero until approximately year 4.

In order to adjust the risk so that negative probabilities did not occur, but also keeping the methodology similar to that described above (of the baseline risk plus age-related risk compounded over 10 years being equal to the 10-year predicted risk), the annual risk increases had to be recalculated so that the risk in the first year could not go below 0.

This was done by building into the model that if a risk entered by the user was below the low levels of risk mentioned above: the risk entered was transformed into a rate, and the annual CV risk increase was based on the difference between zero and twice the annual rate, broken down into 10 increments (and then converted back to a probability). This meant that at very low levels of 10 year risk, the CV risk had a flatter slope in the first 10 years, and then after 10 years the base case annual CV risk increase was applied again (0.03% for men and 0.008% for women) so the slope of the risk over time becomes steeper after the first 10 years. Note the annual increase in risk calculated for low levels of risk was applied across all QRISK2 events (which is all events except heart failure and applied to heart failure based on its relative frequency as a proportion of QRISK2 events). Whereas for risk levels higher than the minimum, the annual risk increases used in the base case were distributed across the CHD events, as previously discussed above. For example Figure 5 shows how this was applied to the risk of 0.5% for 60-year-old men described above in Figure 4.

Figure 4: Risk over time at very low levels of risk (without correction)

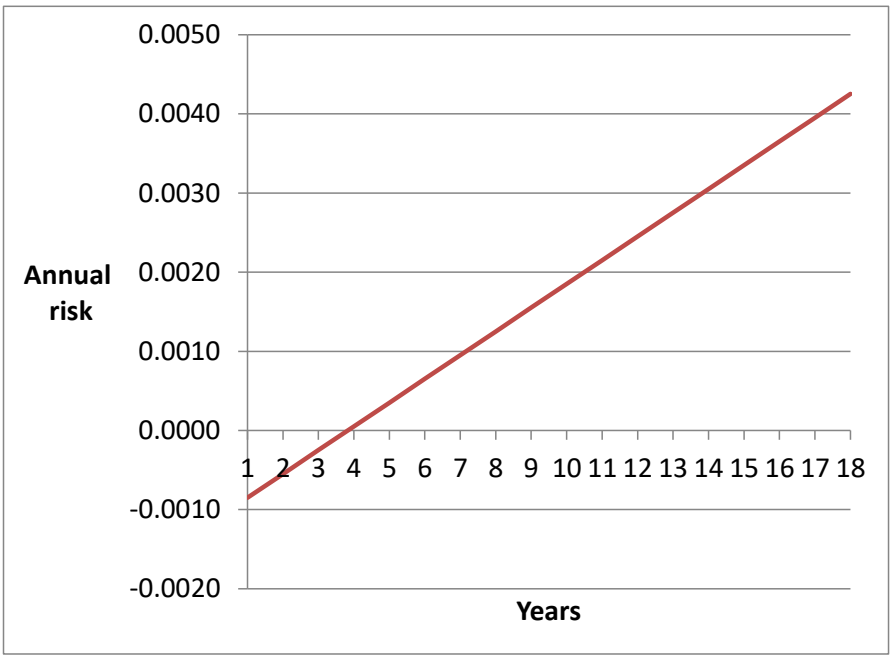
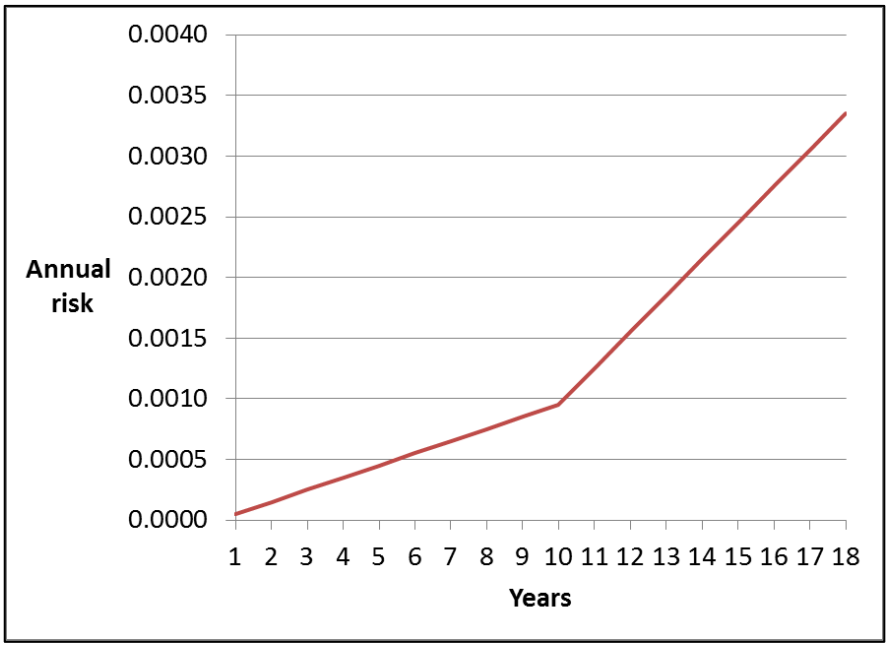


Figure 5: Risk over time at very low levels of risk (with correction)



1.2.3.3.2 Non-cardiovascular mortality

In each 1-year cycle, people in the 'no CV event' state in the model were at risk of death from non-cardiovascular causes and can transition to the death state.

Transition probabilities for non-CV mortality were based on the Office of National Statistics (ONS) life tables for England 2014-16.[41] The proportion of deaths that were non-circulatory were also taken from the ONS and applied to the mortality rates to determine the non-CV mortality rate by age and sex.

1.2.3.3.3 Mortality post-cardiovascular event

In each 1-year cycle, people in the non-fatal CV event states in the model could transition to the death state.

Once people had experienced a non-fatal CV event and entered 1 of the CV event health states, they were attributed a higher mortality rate. Transition probabilities were implemented by applying relevant standardised mortality ratios (SMR) to age-dependant general population mortality rates (all-cause mortality) from England life tables and converting to a probability. SMRs were identified from other models in NICE guidelines and can be seen in Table 4.

Table 4: Standardised mortality ratios for cardiovascular events

Event	SMR (95% CI)	Source
SA	1.95 (1.65-2.31)	Age-adjusted relative risk for death from any cause in men with angina (compared to men free from clinical CHD). 16-year follow-up. Swedish general population sample. Rosengren 1998 [46].
UA	2.19 (2.05-2.33)	Weighted average of SMRs for UA/NSTEMI 1 year in those alive at 6 months with and without new MI. UA/NSTEMI NICE guideline.[28] Validated using Fox et al. age adjusted HR for mortality with UA compared to SA was 1.1.
MI	2.68 (2.48-2.91)	Average of SMRs for men and women. All-cause mortality after first non-fatal MI compared to that expected in the general population. Danish population. Up to 15-year follow up (Bronnum-Hansen 2001).[7]

Event	SMR (95% CI)	Source
TIA	1.4 (1.1-1.8)	Risk ratio for mortality in people with TIA compared to that expected in those without TIA (age and sex matched). UK population. Mean of 3.7-year follow-up. Oxfordshire Community Stroke Project.[16]
Stroke	2.72 (2.59-2.85)	Average of SMRs for men and women. All-cause mortality after first on-fatal stroke compared to that expected in the general population. Danish population. Up to 15-year follow up (Bronnum-Hansen 2001).[6]
HF	2.20 (a)	Chronic heart failure natriuretic peptides decision thresholds model.[38] Based on the SMR used for the preserved ejection fraction heart failure (HF-PEF) population, where annual mortality from a trial with an average of 4-year follow up was compared to the general population annual mortality for the same age group to derive a crude SMR.

(a) CI not reported so a standard error of 10% of the mean was assumed for the probabilistic analysis.

All SMRs except for heart failure were taken from the NICE 2011 Hypertension guideline (CG127) diagnosis model.[30]

For the heart failure SMR, the committee noted a number of reports of varying excess risk with heart failure that could be dependent on different definitions, as well as proportions and severities of reduced ejection fraction heart failure (HF-REF) and preserved ejection fraction heart failure (HF-PEF). HF-REF generally is a post-MI disease, and is exacerbated by concurrent hypertension and tends to have a higher mortality rate than HF-PEF, which is epidemiologically strongly associated with hypertension and obesity. The committee decided that a lower SMR from heart failure was reasonable. Other estimates were higher and included a 4-fold excess risk, which was modelled in the sensitivity analysis.

SMRs were chosen with longer-term follow-ups to reflect an average mortality rate that could be applied to both the event states and post-event states. Ideally, mortality ratios that capture the mortality rate in the year after the event and then mortality rates that do not include the first year after the event would have been more appropriate; however, these were not available. This could mean that the mortality rate immediately after an event may be underestimated in the model, which in turn would underestimate the benefit of treatment from events avoided. However, as the model is inherently conservative by using longer-term mortality and only modelling the first event, this was felt to be reasonable simplification and if anything might mean that treatment is more effective than being shown by the model.

These inputs were incorporated into the probabilistic analysis using lognormal distributions parameterised using the confidence intervals or an assumed standard error where confidence intervals were not available.

1.2.3.4 Relative treatment effects

Treatment effects feeding into the model are based on the only systematic review of RCTs included in the clinical review (Brunström 2018[8]), that compared treatment with no treatment in a population with stage 1 hypertension. Although observational evidence was also available in this population, the systematic review was felt to be of higher quality because it was a large systematic review of RCTs, which are considered the best available evidence.

The Brunström data was also adjusted using age adjustments from Law 2009.[22] This adjustment was performed to take into account the fact that treatment effect may vary by age. The inputs can be seen below in Table 5.

Table 5: Base case relative risks of CV events and CV death

	35-44	45-54	55-64	65-74	75+
CHD events					
Men	0.86	0.84	0.86	0.91	0.90
Women	0.84	0.84	0.86	0.90	0.89
Stroke events					
Men	0.84	0.83	0.86	0.93	0.92
Women	0.81	0.82	0.86	0.92	0.90
Heart failure events					
Men	0.85	0.84	0.87	0.94	0.94
Women	0.82	0.83	0.87	0.93	0.91
Cardiovascular mortality					
Men	0.84	0.83	0.86	0.93	0.92
Women	0.81	0.82	0.86	0.92	0.90

Further discussion on the possible sources of treatment effect that were identified and the age adjustment methodology can be found in the sections below.

The raw relative risks from Brunström[8] (prior to age adjustment) were incorporated into the probabilistic analysis using lognormal distributions. These were parameterised using the confidence intervals for the relative risk reductions.

The CHD relative risk was applied to the MI, stable angina and unstable angina health states. The stroke relative risk was applied to the stroke and TIA health states. The heart failure relative risk was applied to the heart failure health state. The cardiovascular mortality relative risk was applied to the CV death state.

It is noted that the relative risks can go over 1 in the probabilistic analysis, particularly in the older age groups. This is both because the confidence interval around the clinical review relative risks goes over 1 for some of the outcomes and because of the impact of the age adjustment increasing the relative risk (that is, reducing the treatment effect) in the older age groups. Given that the clinical review was a meta-analysis based on many observations, it was considered reasonable that this captured uncertainty appropriately for the base-case analysis. The average of all the simulations will still be the base-case relative risks.

Sensitivity analysis around the relative treatment effect was undertaken as deemed appropriate following discussion with the committee.

Discussion on treatment effect selection

A review was undertaken as part of the guideline to identify the blood pressure or CV risk threshold at which antihypertensive drug treatment should be initiated.

Evidence was only identified for stratifications of blood pressure, not cardiovascular risk. Two studies were included that compared treatment versus no treatment in a stage 1 hypertension population.

Sheppard 2018[48] was an observational study using a large cohort from UK CPRD data. The population was people with stage 1 hypertension but also people at 'low-risk' of cardiovascular disease. Low-risk was defined as excluding people who had a history of CVD and other comorbidities, rather than by classifying people according to their CV risk value. The reason given for this approach was that there was insufficient data to calculate CV risk reliably for each individual. However, an average 10 year CV risk level was reported in the study of 8%. This was based on 20% of the cohort that had a previous risk score reported; 24% that had additional risk factor information to allow a QRISK2 score to be calculated; and

for the remainder age- and sex-standardised characteristics from the Health Survey for England were input into the risk calculator to replace missing data. The average age in Sheppard was 55 with a mean systolic BP of 145 mmHg. This study comes with the limitations associated with observational data, in that it cannot be entirely ruled out that results were affected by confounding. There was also less observation time in the non-exposed group because some people started treatment. Around 40% of the untreated people were prescribed an antihypertensive at some point during follow up. This is likely to have attenuated any benefits by reducing the rate of events in the untreated arm of the trial. This would reduce the likelihood of the study showing any significant benefit, as the study was analysed on an intention-to-treat basis. The results of the Sheppard study showed that there is unlikely to be a benefit in the treatment group compared to the no treatment group in lower risk people with stage 1 hypertension.

Brunström 2018[8] was a meta-analysis of RCTs in people with hypertension and reported results for a primary prevention subgroup, stratified by systolic BP <140 mmHg, 140-159 mmHg (stage 1), and >160 mmHg. The population was reported to have an average age of 63 years (although this is for the overall primary prevention population and not just those with stage 1 hypertension). This means that on age alone, the population on average is unlikely to be very low risk as compared to the average age in Sheppard 2018 of 55. The average systolic BP in Brunström for the stage 1 group alone is unclear, but for the entire primary prevention population as a whole, the mean systolic BP was 154 mmHg. Additionally, the majority of trials labelled as primary prevention in the Brunström meta-analysis had populations with comorbidities such as diabetes and renal disease, which would also increase the average risk. Overall, this leads to the conclusion that the population in Brunström is likely to be of higher CV risk than in Sheppard. Brunström showed a treatment benefit in terms of the magnitude of the relative risk although some relative risks did cross 1.

The overall conclusion from this evidence is that there is uncertainty around the benefit of treatment in lower risk individuals with stage 1 hypertension from observational data, and there is some evidence of benefit in treatment in more intermediate or higher risk individuals with stage 1 hypertension in RCT data. However, there is no single study comparing the benefit of treatment across different risk groups specifically. To the committee's knowledge, there are no existing studies based on RCT data that look specifically at treatment in low risk people; therefore, any existing RCTs or systematic reviews are in intermediate or higher risk individuals. A lack of data in low-risk individuals is likely to be because lower risk individuals by definition would not lead to as many events. Therefore, studies tend to be underpowered and would have to recruit very large cohorts with a substantial follow-up period.

The committee agreed it would be reasonable to assume that relative treatment benefit would be the same regardless of CV risk level, as no strong evidence had been identified to the contrary. Although there is uncertainty around treatment benefit in lower risk individuals with stage 1 hypertension, the committee did not feel confident in assuming different relative risks for different risk groups, which would be mostly assumption based, but decided that they would interpret the low risk subgroup results with caution.

Other sources for treatment effect were also debated, such as the Law 2009 study,[23] which was the source of treatment effect used for the 2011 hypertension guideline diagnosis model. The Law 2009 study had a meta-analysis aspect: this was included in the guideline clinical review for the diastolic blood pressure strata, as it was superseded by the Brunström meta-analysis for the systolic blood pressure strata because Brunström is more up-to-date. The other aspect to Law 2009, was a 2-stage regression, with step 1 based on a meta-analysis of randomised trials that found a relationship between BP and drug dose (Law 2003[24]). And step 2 based on a meta-analysis of cohort studies that found the relationship between BP reduction and disease events by age.[25] The conclusion of the 2-stage regression were predicted relative risks for CHD events and stroke stratified by pre-treatment systolic blood pressure (120–180 in 10 mmHg increments), age (40–90 in 10-year increments), and number and dose of drugs (1–3 drugs, at half or standard dose). The predicted relative risks

are the most useful for the model because they subgrouped by age and number of drugs. It was unclear what populations were feeding into the regression equations that Law 2009 ultimately used, but they were unlikely to be a population with very low risk, for the reasons mentioned previously.

The relative risk reductions reported within Law 2009[23] were much higher than those reported by Brunström[8]. One reason that might explain this is that the two studies have quite different approaches to analysing data. Law was considered to be more comprehensive than Brunström because it subgroups by age and number of drugs but uses statistical methods that may not be valid, as the relative risks are predicted rather than being observed. Whereas Brunström used more up-to-date data and had more participants but is less comprehensive because it only reports overall relative risks that are not sub-grouped by age.

Different treatment effects are likely to impact the model results and the use of more favourable treatment effects (for example, using Law data[23] rather than Brunström[8]) could potentially overestimate the benefit of treatment. Therefore, the committee decided that for treatment effect in the base case, the Brunström data was the most appropriate because RCTs are the gold standard in the hierarchy of evidence. It is a conservative estimate compared to Law and also provides the most up-to-date meta-analysis data.

A sensitivity analysis was undertaken on treatment effect including using data from the Law 2009[23] in a sensitivity analysis, which has more favourable relative risk reductions (see section on sensitivity analyses). Using the Law data in this way also addresses the concern about the uncertainty around the base case relative risks sometimes crossing 1, because the confidence intervals from the Law relative risks do not cross 1. Additionally, the base-case data from Brunström was adjusted to consider that the average level of treatment in the meta-analysis was less intensive than clinical practice, as most included trials were monotherapy trials and the blood pressure reduction between the treatment and control arms of the included trials was fairly small. See section 1.2.4 for more detail on sensitivity analyses.

Age adjustments applied to base case treatment effects

The committee also agreed that relative adjustments between age groups should be incorporated based on the treatment effect data from the Law meta-analysis.[23] The use of different numbers of drugs by age group and sex (see Table 12) were used to derive weighted average relative risks from Law (see sensitivity analysis section for explanation of how the Law data was used and the resulting weighted average relative risks [Table 21]). The adjustments applied to the base case were derived from these weighted relative risks. These adjustments applied to the Brunström data are shown in Table 6. These are based on the relative risks for standard doses.

Table 6: Age adjustments applied to relative treatment effect in model

	35–44	45–54	55–64 (reference)	65–74	75+
CHD events					
Men	1.00	0.98	1.00	1.06	1.05
Women	0.97	0.98	1.00	1.05	1.03
Stroke events					
Men	0.98	0.96	1.00	1.08	1.07
Women	0.94	0.96	1.00	1.07	1.05

Source: Calculated using relative treatment effect data by age and number of drugs from Law 2009[23], and drug use data by age and sex from CPRD data using a committee member contact.

Note: The 55–64 age group is the reference group. The 65–74 and 75-and-older age subgroups both use the relative risks from the 70–79 age group in the Law meta-analysis to derive the age adjustments. There were treatment effects reported in Law for an 80–89 year old age group also, but these were not used to

apply age adjustments to a group older than 75, as there was a trend of increasing relative risks in older age in the Law data. The Brunström relative risks were already felt to be conservative. Note also that anyone on treatment surviving to aged older than 75 will be applied the age 75 age group treatment effect. If the relationship between age and relative risks is to be believed from Law, this means that the older someone is, the less they benefit from treatment. By not applying smaller relative risks to people aged over 75, this means that we may have been modelling treatment as being more effective than it might be. However, the base-case treatment effects are very conservative anyway, so these effects on the model are likely to balance out.

There was no data on relative risk for heart failure by age from the Law meta-analysis, therefore the age adjustments for stroke were applied to the heart failure treatment effect data from the clinical review, as the committee felt that the Law relative risks for heart failure were likely to be more like that of stroke than of CHD. The stroke adjustments from Law led to smaller relative risks in the younger people than if the CHD adjustments were used, but these were still likely to be conservative relative risks. The stroke adjustments were also applied to the cardiovascular death relative risk.

The age adjustments were not made probabilistic.

Note that although the comparator was not necessarily no treatment but included lifestyle modifications and advice no treatment effect was applied to the no antihypertensive treatment arm because such modifications were received by both arms.

1.2.3.5 Adverse events

The model incorporates the following adverse events for people on treatment who were over 60 years of age:

- injurious falls
- acute kidney injury.

The probabilities of these events applied in the model are summarised in Table 7 below. The rationale for the choice of adverse event included and the data source used are discussed below.

Table 7: Adverse event probabilities

Event	Number of events	N	Probability of event (at 3.26 years)	1 year probability
Fall risk	84	3,345	0.025	0.008
AKI risk (aged under 75)	38	3,367	0.011	0.003
AKI risk (aged over 75)				0.008 (a)

(a) Based on the AKI risk for age under 75 multiplied by a relative risk for over 75s (discussed below)

The adverse events associated with antihypertensive treatment tend to be relatively short-term and reversible. They can usually be resolved by changing drugs (either to another drug in the same class or to another drug class). Most adverse events are likely to occur in the initial period following starting antihypertensive treatment. These will then usually be identified as part of the initial monitoring of the drug with the medication amended accordingly. Therefore, some adverse events will not accrue any additional resource use and can be resolved easily. However, there may be adverse events that are more serious and could lead to hospitalisation.

In discussion with the committee, adverse events were felt to be important, particularly in the older age group where they were considered more common than in younger people. Additionally, adverse events were likely to have more of an impact on older people, for example where a fall could lead to a fracture that requires further healthcare resource use and impact quality of life.

The clinical review on initiating treatment identified some observational data on adverse events in people with stage 1 hypertension at lower risk, showing that treatment was associated with more adverse events.[48] As this was observational data, the RCT data from the clinical review on blood pressure targets was used for adverse events and confirmed that treatment causes adverse events. The largest study in the blood pressure targets review for the non-diabetic population was the SPRINT trial.[52] This study is further discussed in the blood pressure targets review (See evidence review D) and is not without its limitations. However, the committee felt that the comparator arm of the SPRINT trial (target of systolic BP 140 mmHg), is roughly in keeping with current practice in terms of antihypertensive treatment intensity, and it agreed that this would be an acceptable source of data on adverse events associated with antihypertensive treatment. A limitation of the SPRINT study is that most of the population were already on treatment; therefore, the probability of adverse events may be being underestimated, as data shows that falls are most likely within 45 days of initiating antihypertensive treatment.[9]

The adverse events being focused on are acute kidney injury and injurious falls. Within the SPRINT trial, these were adverse events that were recorded if they led to a hospital admission and were considered serious.

The adverse event risks were applied only to those aged 60 and over on treatment in the model (in other words when someone reached the age of 60, even if they started treatment earlier). This is both because adverse events were considered to be more frequent in older people, and because the average age of people in SPRINT was over 60. In general, the population in trials tends to be older, so adverse event rates associated with antihypertensive treatments in younger people is uncertain. Note that the adverse events were applied to all those over the age of 60 on treatment, which also includes those who start treatment because of a CV event in the no treatment arm.

These have been made probabilistic using the beta distribution. This is bounded by 0 and 1.

It was also discussed how adverse events were likely to be even more common in those aged over 75. The SPRINT study population had around 30% older than 75. There have been several follow up publications of SPRINT that have looked at the data in different ways and in different subsets of the main population. One particular study looked specifically at AKI events and compared the AKI events in those over and under 75.[45] The ratio of AKI events in the standard treatment arm for those over 75 to those under 75 was found to be 2.29. This ratio was applied to the probability of an AKI in the base case for those over 75.

In a sensitivity analysis, this increase in AKI risk for over 75s was also applied to the probability of a fall. Additionally, adverse events were omitted from the model to see what impact this has.

1.2.3.6 Utilities

1.2.3.6.1 General population quality of life

Quality of life weights (utilities) were applied to people in the model based on general population estimates stratified by age and sex. These were taken from analysis of the Health Survey for England dataset 2014.[42] These can be seen below in Table 8.

Table 8: General population utility estimates

Sex	Age	Mean	Std. Err
Male	35-44	0.895	0.008
	45-54	0.879	0.008
	55-64	0.848	0.010
	65-74	0.846	0.010

Sex	Age	Mean	Std. Err
	75+	0.791	0.013
Female	35-44	0.890	0.007
	45-54	0.868	0.007
	55-64	0.806	0.011
	65-74	0.814	0.010
	75+	0.759	0.012

General population utilities were incorporated into the probabilistic analysis using beta distributions. This is bounded by 0 and 1 – although utility can technically go below 0, the values being used here are far from 0, so this was considered reasonable.

1.2.3.6.24 Quality of life for health states

It was assumed that having hypertension does not reduce quality of life in itself, as it is generally asymptomatic. Reductions in quality of life were, however, applied once a person had experienced a cardiovascular event. Quality of life weights associated with cardiovascular events were applied multiplicatively to the general population weights. The values used were from the NICE Lipids model.[34] These are summarised in Table 9 with the original data sources that were cited.

Table 9: CV event utility multipliers

	Utility multiplier	Standard error	Source
Well	1		By definition
Stable angina	0.808	0.038	Melsop 2003.[27] (a)
Post-stable angina	0.808	0.038	Melsop 2003.[27] (a)
Unstable angina	0.770	0.038	Goodacre 2004,[18] Ward 2005 [39]
Post-unstable angina	0.880	0.018	2008 Lipid modification guideline. [35]
MI	0.760	0.018	Goodacre 2004,[18] Ward 2005 [39]
Post-MI	0.880	0.018	Tsevat 1993.[51]
TIA	0.900	0.025	Lavender 1998.[21]
Post-TIA	0.900	0.025	Lavender 1998.[21]
Stroke	0.628	0.040	Tengs 2003,[50] Youman 2003[54]
Post-stroke	0.628	0.040	Tengs 2003,[50] Youman 2003[54]
Heart failure	0.683	0.020	Davies 2006.[14]
Post-heart failure	0.683	0.020	Davies 2006.[14]
CV death	0		By definition
Non-CV death	0		By definition

(a) Derived from the paper by dividing the time trade-off score from the angina group by the time trade-off score from the non-angina group (7.03/8.70).

Cardiovascular event utilities (except well and dead) were incorporated into the probabilistic analysis using beta distributions.

1.2.3.6.36 QALY loss due to adverse events

The quality of life decrements for adverse events and duration they are applied for (leading to total QALY losses) are summarised in the table below. Discussion of the inputs and sources are detailed further below.

Table 10: QALY loss from adverse events

Input	Value
Fall utility loss	-0.343
AKI utility loss	-0.323
Duration of utility loss	4 weeks
Fall QALY loss	-0.026
AKI QALY loss	-0.025

For AKI, the utility value associated with AKI was based on the utility of renal failure (0.525), taken from the Sullivan catalogue of EQ-5D utilities.[49] This was the same utility attached to an AKI in the NICE AKI guideline model.[32] The utility from the Sullivan catalogue was based on an average age of 60 years (rounded up to the nearest 10). The decrement in quality of life from an AKI used in this model was derived by subtracting 0.525 from the general population utility associated with a 60-year-old in the model. This led to the decrement in the table.

The utility loss associated with a fall was based on that of a hip fracture, and taken from a systematic review on utilities associated with Osteoporosis.[44] This found that the utility loss at 4 months was 0.343.

The quality of life decrement from adverse events will be applied for 4 weeks in the model. Other models on antihypertensive treatment that also included adverse events applied utility loss for a similar amount of time (for example, the SPRINT [US] economic evaluation[4]).

It is noted that because in the model people who have had CV events are also at risk of adverse events, as they would still be on antihypertensive treatment, then the utility decrements for adverse events may not in fact be additive. For example, someone who already has a reduced quality of life because of a CV event may not find having a fall or AKI as impactful on their life as someone who has not had a CV event. This issue may also apply to the effect of adverse events for older ages, as older people who have lower quality of life due to various factors such as other comorbidities and therefore adverse events may not have as much of an impact on their overall quality of life. Therefore, it is acknowledged that there may be an overestimation of the impact of adverse events in the model. However, particularly for falls, the utility value used was that of a longer time period after the event (4 months) than the period it will be applied in the model (4 weeks), so as not to use a very low utility value, even though utilities at around 1 week were also available. In a sensitivity analysis, the utility loss from a fall will be applied for 4 months instead of 4 weeks.

1.2.3.7 Resource use and costs

1.2.3.7.1 Adverse event costs

The costs used for adverse events are summarised in Table 11 below. Discussion of the inputs and sources are detailed further below.

Table 11: Adverse event resource use and costs

Event	Resource use	Unit cost	Source
Fall	From the model in the falls in older people guideline, for a severe fall the following resources were included: • A&E attendance • ambulance journey • outpatient follow up (trauma and orthopaedic)	£506	Resource use from: Falls: assessment and prevention of falls in older people, NICE CG161 (2013).[36] Costs from NHS reference costs 2016/17.[17]

	The above does not include hospitalisation, as this would depend on the length of stay. Cost per hospital day	£693	Weighted average of all healthcare resource group (HRG) related inpatient activity currencies – elective, non-elective, excess bed days and day case. From NHS reference costs 2016/17.[17]
	Length of stay	2.7 days	Kenny 2002[20]
Total		**£2,378**	
AKI	HRG code: LA07 Acute Kidney Injury with/without interventions	**£1,941**	NHS reference costs 2016/17. Weighted average of non-elective short and long stay, including complications and excess bed days.[17]

The NICE guideline on falls in older people (CG161)[36] was searched to identify the average cost of a fall. As the type of fall included in the model was described as an injurious fall in the SPRINT study and led to hospitalisation, this was considered to be similar to a severe fall as defined in CG161. The resource use costed as part of a severe fall included an A&E attendance, ambulance journey, and a trauma and orthopaedic outpatient follow-up (assumed to be non-consultant led, non-admitted face-to-face, as it wasn't defined in CG161). Up-to-date costs for these components were identified from NHS reference costs 2016/17.[17]

This, however, does not include the cost of the hospitalisation on the ward or any subsequent procedures. Specific NHS reference costs were not available for a fall and so the committee agreed that a reasonable approach would be to use average cost per day in hospital combined with estimated length of stay for a fall to estimate the cost of a hospitalisation.

The average cost of a day in hospital was calculated from NHS reference costs and was the weighted average of all HRG related inpatient activity currencies – elective and non-elective activity with associated excess bed day costs and day-case costs. This gave an average cost per bed day of £693.

The average length of stay in hospital following a fall was taken from a study from 2002 that reported an acute length of stay of 2.7 days in a dedicated falls facility for older adults.[20] Data is limited on length of stay following falls, as most published data tends to focus on additional length of stay from falls that happen in hospital. The committee discussed how it is difficult to define an average length of stay, as on the one hand those who have a fall because of their hypertension medication may have a shorter length of stay because the syncope can be dealt with by correcting the medication; although on the other hand, some people may have complications and co-morbidities that lead to a longer length of stay. Additionally, concern about destination upon discharge can lead to longer lengths of stay. Some data from Taunton and Somerset NHS foundation trust identified through committee member contact found an average length of stay of 8.6 days for those admitted for a fall aged over 65 years. This higher value was tested in a sensitivity analysis.

The cost of an AKI hospitalisation was based on the AKI HRGs from NHS reference costs. No additional costs associated with AKI were included (such as dialysis), as the committee thought it would be very uncommon that AKI from antihypertensive treatment would lead to dialysis.

These costs were not made probabilistic as they were based on national sources from NHS reference costs. The length of stay in hospital for falls was also not made probabilistic but this was tested in a sensitivity analysis.

1.2.3.7.21 Drug costs

The cost of hypertension drug treatment was applied to all alive people (that is those who had and had not experienced a CV event) in the treatment arm. It was applied just to those that had experienced a CV event in the no-treatment arm. The costs used in the model are summarised in Table 12 and the basis for these costs are described below.

Table 12: Drug costs

		Men				Women			
Age	Treatment	1	2	3+	Average	1	2	3+	Average
35-44	No. drugs (%)	61%	31%	8%		62%	28%	11%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£13.17	£26.72	£40.28	£19.66	£13.17	£26.72	£40.28	£19.77
45-54	No. drugs (%)	53%	33%	14%		58%	32%	10%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£13.17	£26.72	£40.28	£21.48	£13.17	£26.72	£40.28	£20.15
55-64	No. drugs (%)	44%	38%	18%		51%	35%	13%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£13.56	£26.72	£40.28	£23.35	£13.56	£26.72	£40.28	£21.73
65-74	No. drugs (%)	39%	39%	22%		44%	38%	18%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£13.56	£26.72	£40.28	£24.59	£13.56	£26.72	£40.28	£23.28
75+	No. drugs (%)	38%	40%	22%		41%	39%	20%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£13.56	£26.72	£40.28	£24.79	£13.56	£26.72	£40.28	£24.10

A= ACE inhibitor/ARB; C = calcium channel blocker; D = diuretic
Source: Percentage of people on 1, 2 or 3 drugs based on committee member data on the prescription of medication and changes over time since the last hypertension guideline and on data from 27 GP practices using CPRD data; Drug type used based on guideline recommended treatment algorithm; Costs based on ramapril 10 mg (A), amlodipine 10 mg (C), indapamide 2.5 mg (D) and BNF costs[19].Costs updated in November 2018.

Typical average antihypertensive drug costs were calculated taking into account the percentage of people on 1, 2 or 3 plus drugs by age band and sex based on data on the prescription of medication and changes over time since the last hypertension guideline and on data from 27 GP practices from the CPRD database (through a committee member contact).

For each age-band, typical drug classes (angiotensin-converting enzyme [ACE] inhibitor or angiotensin II receptor blockers [ARB], calcium channel blocker [CCB] and diuretic) were assigned when on 1, 2 or 3 drugs based on the guideline recommended treatment algorithm.

Costs for each class were based on BNF costs for the most commonly used drug in each class for ACE inhibitor or ARB and CCB drugs and on committee opinion for a diuretic. This was because the guideline recommends a specific type of thiazide-like diuretic. Committee members provided the optimal doses: Ramipril 10 mg (ACE inhibitor), amlodipine 10 mg (CCB), indapamide 2.5 mg (thiazide-like diuretic).

The percentages of people on 1, 2 or 3 drugs varied in the probabilistic analysis. These were incorporated into the probabilistic analysis for each age group using Dirichlet distributions.

Drug costs were not subject to probabilistic analysis as these were taken from standard national sources. They were, however, varied deterministically being varied by 50% up and down in sensitivity analyses.

1.2.3.7.39 Monitoring costs

As well as the costs of the drug themselves, there is also monitoring that is required. The monitoring resource use and costs applied in the model are summarised in Table 13 by type and number of drugs that vary by age and sex (as discussed in the drug costs section above). The basis for these costs is discussed below.

Table 13: Total monitoring costs

		Men				Women			
Age	Treatment	1	2	3+	Average	1	2	3+	Average
35-44	No. drugs (%)	61%	31%	8%		62%	28%	11%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person – year 1	£96	£142	£188	**£118**	£96	£142	£188	**£118**
	Average cost/person – subsequent years	£76	£76	£76	**£76**	£76	£76	£76	**£76**
45-54	No. drugs (%)	53%	33%	14%		58%	32%	10%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person – year 1	£96	£142	£188	**£124**	£96	£142	£188	**£119**
	Average cost/person – subsequent years	£76	£76	£76	**£76**	£76	£76	£76	**£76**
55-64	No. drugs (%)	44%	38%	18%		51%	35%	13%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	

Age	Treatment	Men				Women			
		1	2	3+	Average	1	2	3+	Average
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person – year 1	£84	£142	£188	**£124**	£84	£142	£188	**£118**
	Average cost/person – subsequent years	£76	£76	£76	**£76**	£76	£76	£76	**£76**
65-74	No. drugs (%)	39%	39%	22%		44%	38%	18%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person – year 1	£84	£142	£188	**£129**	£84	£142	£188	**£124**
	Average cost/person – subsequent years	£76	£76	£76	**£76**	£76	£76	£76	**£76**
75+	No. drugs (%)	38%	40%	22%		41%	39%	20%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person – year 1	£84	£142	£188	**£130**	£84	£142	£188	**£127**
	Average cost/person – subsequent years	£76	£76	£76	**£76**	£76	£76	£76	**£76**

A= ACE inhibitor; C = calcium channel blocker; D = diuretic
Source: Percentage of people on 1, 2 or 3 drugs based on committee member data on the prescription of medication and changes over time since the last hypertension guideline and on data from 27 GP practices using CPRD data; Drug type used based on guideline recommended treatment algorithm.

In the no drug treatment arm, annual blood pressure monitoring was included in line with the current recommendations of the guideline for people with stage 1 hypertension. This was assumed to be with a consultation with a GP. This is the same for all years.

Resource use – first year

For those on drug treatment, it was assumed that there would be more consultations required for monitoring with this being more frequent in the first year of being on treatment. The number of consultations for those on treatment was separated by the number of drugs being taken (see Table 14). This was based on assumptions from the committee. Although the exact frequency of consultations for people on treatment is not known, a study by Xu et al 2015[53] found that the average follow-up frequency after intensification of medication was about 1.3 months and mean time to intensification of medication, after blood pressure was found to be high, was around 6 months supporting that monitoring is more frequent after a change in medication (which probably also applies to introducing medication).

Table 14: Number of consultations associated with treatment/no treatment – year 1

	No treatment	1 drug	2 drugs	3 drugs
Number of consultations	1	2	3	4

The number of consultations in the first year of treatment will be tested in sensitivity analysis by doubling these.

Tests were also included to monitor for adverse events associated with the drugs. Tests include clinical biochemistry of urea and electrolyte testing as well as urinary albumin:creatinine ratio. No tests were assumed for the no treatment arm. For the first year, resource use was separated by type of drug for the tests involved (as some classes of drugs require more monitoring than others because they are known to cause more adverse events; see Table 15. ACE inhibitor or ARB drugs and thiazides require more clinical biochemistry monitoring than for CCBs. A urine test testing the albumin:creatinine ratio would also be undertaken after starting drug classes A and D, as they are known to have potential impacts on the kidneys. The committee provided the resource use.

Table 15: Number of tests associated with treatment/no treatment – year 1

Tests		No treatment	A drugs	C drugs	D drugs
	Clinical biochemistry	0	4	1	2
	Albumin: creatinine ratio	0	1	0	1

Note: A drugs: ACE inhibitor or ARB drugs, C drugs: calcium channel blockers, D drugs: diuretics.

When treatment begins, in reality, people will move up the steps of treatment over time; however, in the model, this process was simplified by applying all first-year costs of the different steps of treatment (based on the distribution of people on different numbers of drugs) in the first year of the model.

Resource use - Subsequent years

Resource use for subsequent years can be found below in Table 16.

Table 16: Monitoring associated with treatment/no treatment – subsequent years

		No treatment	All drugs
Tests	Clinical biochemistry	0	1
	Albumin:creatinine ratio	0	0.2
No of consultations		1	1.87

For subsequent years there was only 1 set of monitoring regardless of how many drugs someone was on; therefore, the resource use involved in subsequent years was grouped together.

The average number of consultations when on treatment was calculated based on CPRD data on the number of GP consultations in hypertensive people in 2016, based on data obtained through a committee member contact[26]. This applies regardless of how many drugs someone was on.

An annual clinical biochemistry test was assumed for everyone on treatment, and 20% of people on treatment in subsequent years were assumed to have their albumin:creatinine ratio tested because it would be mainly the diabetic population of a general hypertensive population that would have this test undertaken on an annual basis.

Additionally sensitivity analysis tested a scenario where a suitably qualified GP practice nurse undertook the consultations rather than a GP.

Unit costs

Unit costs of the resource use for monitoring can be found below in Table 17.

Table 17: Unit costs associated with monitoring

Resource	Unit cost	Source
GP consultation	£38	GP per person contact lasting 9.22 minutes, Including direct care staff costs and qualifications. PSSRU 2017.[12]
Urea and Electrolytes	£4.13	Made up of: • £3: Direct access phlebotomy cost. NHS reference costs 2016/17[17] • £1.13: Direct access Clinical Biochemistry cost. NHS reference costs 2016/17[17]
Albumin: creatinine ratio	£3.33	Albumin:creatinine ratio, inflated from CKD guideline from 2011 cost to 2015/16 cost. [33] PSSRU 2017[12],

The directly accessed pathology services from NHS reference costs 2016/17 are averages of the costs involved in providing pathology services in the NHS, when carried out independently from an admission or attendance (for example, when a person is referred by a GP for a test or self-refers).[17] Costs that are submitted by trusts can vary depending on whether the service is hospital or community based, and the average captures this.

Monitoring unit costs were not subject to probabilistic analysis as these were taken from standard national sources.

1.2.3.7.40 CV health state costs

The costs assigned to the CV health states in the model are summarised in Table 18. The basis for these costs are discussed below.

Table 18: Health state costs

State	Cost (annual)	Source
Stroke (initial)	£23,076	Xu et al 2016 – SSNAP project inflated to 2016/17.[47]
Post-stroke	£5,183	Xu et al 2016 – SSNAP project inflated to 2016/17.[47]
TIA	£1,746	Danese 2016 inflated to 2016/17.[13]
Post-TIA	£587	Danese 2016 inflated to 2016/17.[13]
Myocardial infarction	£4,641	Danese 2016 inflated to 2016/17.[13]
Post-MI	£768	Danese 2016 inflated to 2016/17.[13]
Stable angina	£908	NHS reference costs 2016/17. Total HRGs. EB13. Weighted average of the complication and comorbidity codes. [17]
Post-stable angina	£273	Assumed same as post unstable angina state.
Unstable angina	£2,336	Danese 2016 inflated to 2016/17.[13]
Post-unstable angina	£273	Danese 2016 inflated to 2016/17.[13]
Heart failure	£2,719	Danese 2016 inflated to 2016/17.[13]
Post heart failure	£706	Danese 2016 inflated to 2016/17.[13]

Source/Note: All published costs that were inflated above were inflated to 2016/17 costs using the Hospital & Community Health Services (HCHS) Pay & Prices Index (PSSRU 2017)[12].

Sources of cost data were identified by reviewing sources used in other similar cardiovascular models (NICE guideline or TA models or published economic models) and through non-systematic online searches to identify newer publications.

Costs of stroke were based on Xu 2016[47] who undertook a patient level simulation using audit data from the UK Sentinel Stroke National Audit Programme to generate estimates of

the financial burden of Stroke to the NHS and social care services. The estimates of costs attributable to stroke from resulting health and social care provision were estimated up to 5 years after the first stroke. The total of 1-year and 5-year costs were reported with NHS and social care costs being reported separately. Recurrent strokes were also included in the costs. For the event state cost in the model, the 1-year total costs from the study were used. The 1-year costs included both local authority and private social care costs, as it was not possible to disaggregate the two. Therefore, it is acknowledged that this may be an overestimate of the cost of stroke to the NHS, and this will be tested in a sensitivity analysis. The costs of the post-event state was calculated based on the difference in costs between the 1-year and 5-year period, so as not to double count, and the difference in average life-years between years 1 and 5 in order to derive the cost per-life-year. The 5-year cost included only local authority social care costs, as these were reported separately in the report.

Danese 2016 aimed to characterise the costs to the UK National Health Service of cardiovascular (CV) events among individuals receiving lipid-modifying therapy. It was a retrospective cohort study that used Clinical Practice Research Datalink records from 2006 to 2012 to identify individuals with their first and second CV-related hospitalisations (first event and second event cohorts). Costs were reported for TIA, unstable angina, MI, and heart failure. The study only included healthcare costs. Costs after each CV event were estimated, and the incremental difference from the period before the first CV event was calculated. The follow-up period was 36 months after the event with costs broken down into the first 6 months, and 7–36 months' time. Costs reported here for the event state are made up of the (first event) 6-month cost plus one fifth of the 7–36-month costs to equate to a crude 12-month cost. Post-event costs are made up of the remainder of the 7–36-month cost, that is, the 13–36 month portion. Although this is for more than a year, these costs were felt to be conservative anyway, as they do not include social care costs or the cost of repeat events.

All published costs above were inflated to 2016/17 costs using the Hospital & Community Health Services (HCHS) Pay & Prices Index.[12]

The cost for the stable angina event state was based on NHS reference costs. The Chest pain of recent onset NICE guideline 2016 (CG95[29]) recommendations state the resources that should be involved in diagnosing stable chest pain. These resources include clinical assessment, blood tests, CT angiography, and potentially other non-invasive functional imaging tests such as myocardial perfusion scintigraphy. NHS reference costs reports HRG codes for angina (EB13A-D), taking the weighted average of the complication and comorbidity codes of the total HRGs for these codes equals a cost similar to that of the different components involved in diagnosing stable angina costed separately; therefore, the committee agreed that the NHS reference costs value would be appropriate. Although this would not cover management costs outside of the acute admission in the remainder of the first year of the event, the post-event-state cost was felt to capture the majority of the subsequent management.

For the post-stable angina state, the NICE guideline on Stable angina: management (CG126; 2016[31]) undertook a cost effectiveness analysis comparing coronary artery bypass graft (CABG) with percutaneous coronary intervention (PCI), and reported the resources (and cost) of medical treatment associated with ongoing angina. These costs were discussed with the committee but were felt to be an underestimate because they only include drugs, and the committee felt it was likely that it should also include several consultations. Therefore, the committee agreed that the cost post-stable angina should be assumed to be the same as the post-unstable angina cost.

These costs were not incorporated probabilistically into the analysis. They were varied in sensitivity analyses by halving and doubling the costs to look at the impact of higher and lower costs being used (see section 1.2.4).

1.2.4 Sensitivity analyses

The sensitivity analyses described below were deterministic unless otherwise stated.

1.2.4.1 Finding specific risk levels at which treatment is cost effective

For each age group and sex, at what exact risk level treatment becomes cost-effective was explored.

The minimum QRISK2 levels by sex and age group were identified to assess whether the risk levels being explored were clinically feasible. In other words, what would the likely risk level be of the healthiest possible person of a certain age and sex with stage 1 hypertension? These levels are shown in Table 19 and are based on the QRISK2-2017 version of the calculator.

The 'male' and 'female' columns were based on systolic BP of 140 mmHg for all age groups and a total cholesterol: High-density lipoproteins (HDL) cholesterol ratio of 2.5. They were not on treatment. All other variables within the calculator were left blank.

For the average risk level column, the average level of systolic BP for untreated stage 1 hypertensives was used which was found to be 150 mmHg[43] to reflect a more typical population for each age group. A body mass index (BMI) of 25 kg/m^2 (composed of height 167 cm and weight 70 kg), and a total cholesterol:HDL cholesterol ratio of 4, were also assumed. This was based on a 'typical' population from Nottingham (based on personal contact from a committee member).

Therefore, for example for males age 60 years, if treatment was found to be cost-effective even at 5%, then this tells us that such treatment is cost-effective regardless of risk because all males aged 60 years or more have a CV risk higher than 5%. The exact risk level that treatment becomes cost-effective would therefore not be relevant as treatment to anyone that age would be cost-effective.

Table 19: Minimum and average QRISK2 levels

Age	Male (minimum risk)	Male (average risk level using 'typical data')	Female (minimum risk)	Female (average risk level using 'typical data')
40	1.5%	2.1%	0.9%	1.3%
50	4.0%	5.7%	2.3%	3.2%
60	8.5%	12%	5.3%	7.2%
70	16.4%	22.3%	11.7%	15.6%
75	22.3%	29.6%	17.0%	22.4%

1.2.4.2 Results from other age groups (probabilistic)

Results for the age 40, 50, 70, and 75 age groups for both sexes and all risk levels.

1.2.4.3 Differential treatment durations (probabilistic)

As has been discussed in section 1.2.2.2, it was seen as too complex to model underlying blood pressure, CV risk and other factors that people with stage 1 hypertension may develop over time in order to model the situation where people exiting from stage 1 hypertension become eligible for treatment for other reasons. Therefore, to capture the simplification that those on no treatment remained on no treatment for the rest of their lives, treatment started for those on no treatment at selected time frames in the model.

The differential time periods chosen were dependent on the starting age of the model, as a younger cohort (aged 40 or 50 years) may not develop criteria that make them eligible for treatment for another decade, but a 70-year-old is much more likely to become eligible for treatment after a shorter period of time (see Table 20). The time points tested were somewhat arbitrary, as it is not known when someone might develop other risk factors. Therefore, this analysis was exploratory to assess the impact of omitting the complexities around developing other risk factors that made an individual eligible for treatment.

Table 20: Differential treatment durations tested by age group

Age subgroup	Durations of differential treatment tested
40, 50	1, 5, 10 and 20 years
60	1, 5 and 10 years
70, 75	1 and 5 years

Treatment effect

1.2.4.4 SA1: Using treatment relative risks from Law 2009 (probabilistic)

Coronary heart disease and stroke

The Law meta-analysis[22] reported relative risks for CHD events and stroke, based on regression, stratified by pre-treatment systolic blood pressure (120–180 in 10 mmHg increments) or pre-treatment diastolic blood pressure (75–110 in 5 mmHg increments), age (40–90 in 10-year increments), and number and dose of drugs (1–3 drugs, at half or standard dose). It was considered important to capture the fact that the relative risk reduction will change with the number of medications. Average risk reductions were calculated for use in the model for each age and sex stratified subgroup based on the average untreated systolic blood pressure in each group, and the split between usage of 1, 2 and 3 drugs. In the base case, it was assumed that standard doses were used.

For average untreated stage 1 blood pressure for each age group and sex: The Health Survey for England (HSE) 2006 dataset[43], which captured detail on prevalent cardiovascular disease/risk factors, and for which there has not been a dataset as detailed on cardiovascular disease since, was analysed. Alongside this, the English Longitudinal Study of Ageing (ELSA) was analysed.[2] This is a study on ageing of people over 50 years. It takes place every 2 years and is based on participants selected from the HSE and some additional participants. It captures bio-medical data every 4 years by a qualified nurse.

The HSE was analysed by identifying those who were hypertensive untreated with only a systolic BP within the stage 1 range. Wave 6 of the ELSA, which recorded information in 2012/13 and was the latest dataset to have detailed information on whether people were taking drugs for hypertension, was analysed by finding only those people who had stage 1 blood pressures but were not taking drugs for hypertension.

Both datasets found that if we round to the nearest 10 mmHg, the average blood pressure of every age group will always round to systolic BP 150 mmHg. This provided evidence to support the rationale that using the relative risks from Law 2009 based on pre-treatment systolic blood pressure of 150 mmHg, for all age groups, and sexes, would be a reasonable approach.

The split between usage of 1, 2 and 3 drugs was based on data on the prescription of medication and changes over time since the last hypertension guideline and on data from 27 GP practices using CPRD data (obtained through committee member contact). See Table 12.

CHD events in the meta-analysis were defined as 'fatal or non-fatal myocardial infarction or sudden cardiac death but excluding "silent" infarcts'. In the model, this risk reduction was applied to all CHD events (MI, UA, SA and CHD death). Stroke was defined in the meta-analysis as 'one or more strokes'. In the model, this risk reduction was applied to all stroke events (stroke, TIA, stroke death).

The relative risks used in the model are shown below in Table 21.

Table 21: Relative risk of CHD and stroke events with antihypertensive treatment

Age	Relative risk for CHD events		Relative risk for stroke events	
	Male	Female	Male	Female
35–44	0.65	0.65	0.55	0.55
45–54	0.64	0.65	0.54	0.56
55–64	0.65	0.67	0.56	0.58
65–74	0.69	0.70	0.61	0.62
75+	0.69	0.69	0.60	0.61

(a) The RRs from the meta-analysis were taken from the following age groups: for the 35–44 age subgroup, the age 40–49 RRs were used; for the 45–54 age subgroup, the 50–59 RRs were used; for the 55–64 age subgroup, the 60–69 RRs were used; for the 65–74 and 75 age subgroups, the 70–79 RRs were used.

Relative risk inputs were incorporated into the probabilistic analysis using lognormal distributions. These were parameterised using the confidence intervals for the relative risk reductions.

Heart failure

Law 2009 did not report heart failure treatment effect in the same level of detail as CHD and stroke treatment effects: there was no breakdown by age and number of drugs. The committee view was that heart failure was considered to be impacted differently by antihypertensive treatment than the events that make up coronary heart disease (MI, stable and unstable angina) and is possibly more similar to stroke in terms of treatment effect. However, Law did report heart failure relative risks by both class of monotherapy and for combination therapy. See Table 22.

Table 22: Heart failure relative risks reported in Law 2009

Class of drug	RR	lower CI	upper CI
Single drug therapy:			
A	0.74	0.68	0.81
C	0.81	0.69	0.94
D	0.59	0.45	0.78
Combination therapy	0.57	0.36	0.92

From table 6, Law 2009.[23]

Given this data, and in order to be in keeping with the format of the CHD and stroke data from Law, the single drug relative risks were weighted by the distribution of drugs for those on 1 drug for each age groups and sex (from Table 12). In addition, for those on more than 1 drug the combination therapy relative risk applied. These relative risks were then weighted by the distribution of people on 1, 2 and 3 plus drugs for each age group and sex from Table 12.

This leads to the weighted relative risks for heart failure, incorporating the treatment effect by number of drugs, in Table 23.

Table 23: Relative risks of heart failure events with antihypertensive treatment

Age	Relative risk for heart failure events	
	Male	Female
35–44	0.67	0.68
45–54	0.66	0.67
55–64	0.63	0.64
65–74	0.62	0.63
75+	0.62	0.62

The heart failure risks follow a different pattern to those of CHD and stroke from Law, as the CHD and stroke relative risks were based on multiple regression steps, as discussed earlier, which led to a pattern of treatment being less effective in older age groups. Whereas, the heart failure data is based on meta-analyses and does not break down treatment effect by age, but treatment effect by age has been derived here by weighting the relative risks reported by number (and type) of drugs being used by age group. These differences between events imply that treatment is more effective at avoiding heart failure events in older people than avoiding other types of events.

The heart failure relative risks were made probabilistic using the lognormal distribution and were parameterised using the confidence intervals for the relative risk reductions.

CV mortality

Cardiovascular mortality relative risks from Law[23] were taken to be the same as the relative risk of CHD and stroke events, as the paper reported the events as fatal or non-fatal.

In order to have a single relative risk for CV death, the CHD and stroke relative risks were weighted according to the proportion of CV deaths that were CHD death and cerebrovascular deaths. These proportions were derived as part of the distribution of events for baseline risk, from Ward 2005.[39] The relative risks derived for CV death can be seen below.

Table 24: Relative risks of CV death with antihypertensive treatment

Age	Relative risk for heart failure events	
	Male	Female
35–44	0.62	0.59
45–54	0.61	0.60
55–64	0.62	0.61
65–74	0.66	0.66
75+	0.64	0.63

Although it is possible that there may be some double counting by using the same treatment effect for events as well as death, the Brunström data[8] used in the base case reported similar relative risks for CV mortality as for the events, which adds some reassurance that using the same relative risks from Law for events and death was an appropriate approach.

1.2.4.5 SA2: Adjusted base case data (Brunström) to take into account more medication (probabilistic)

The Brunström[8] meta-analysis, which was used as the source of treatment effect in the base case, was based mostly on studies that used a single drug. The committee's opinion was that this would lead to a blood pressure reduction, and therefore, by association, a treatment

effect that would not fully reflect the treatment benefit that would be achieved in practice, as most people would be prescribed more than 1 drug.

To address this, the Brunström relative risks were adjusted to take into account the effect of more medication. The method of dose-adjustment is based on that described in Law 2009.[23] This paper attempted to answer many questions and to follow a sequence of steps to create a link between blood pressure reduction and reduction in cardiovascular events depending on the number of drugs being used. The paper calculated the reduction in pre-treatment blood pressure from 1 drug and quantified this using regression with the same equations applied sequentially as the number of drugs increased. The next step involved working out reduction in disease events based on a specific reduction in blood pressure. This was based on a published meta-analysis of cohort studies that showed that cardiovascular mortality plotted on a logarithmic scale against blood pressure on an arithmetic scale was well fitted by straight lines, indicating a constant proportional change in risk for a specified change in blood pressure (see section 1.2.3.4 for more explanation on this).

The pre-treatment blood pressure was taken to be 150 mmHg, as this was identified as the average systolic BP of untreated stage 1 hypertensives,[43] regardless of age. The estimated reduction in systolic BP by pre-treatment systolic BP and the number and dose of drugs was taken from Law 2009[23] (based on standard doses) and is reported in columns 2 and 3 of Table 25.

Table 25: Estimated and proportional SBP reduction based on number of drugs (Law 2009)

Pre-treatment systolic BP	No. of drugs	Estimated reduction in systolic BP (a)	Proportional systolic BP reduction in reference to 1 drug (b)
150	1	8.7	
150	2	16.5	1.90
150	3	23.6	2.71

(a) Taken from table 3, Law 2009. [23].
(b) Calculated.

The relative risks from the Brunström paper were assumed to be the relative risks associated with a single drug. The systolic BP reduction in Brunström was 4.6 mmHg in the baseline systolic BP 140–149 mmHg group, which also confirmed that this is based on low-intensity treatment because it is lower than the reduction in systolic BP reported in Law for 1 drug. The Brunström relative risks (for CHD, stroke, HF and CV mortality) were then raised to the power of the proportional systolic BP reductions to derive the relative risks for each event based on 1, 2 and 3 drugs. This was based on the method described by Law.[23]

These relative risks were then weighted by the distribution of people on 1, 2 and 3 plus drugs by age and sex to derive an overall weighted average relative risk by age and sex. These can be seen in Table 26.

Table 26: Dose adjusted Brunström relative risks, by age

Outcome	Sex	35–44	45–54	55–64	65–74	75
CHD	Men	0.81	0.80	0.78	0.77	0.77
	Women	0.81	0.81	0.80	0.78	0.78
Stroke	Men	0.81	0.80	0.78	0.77	0.77
	Women	0.81	0.81	0.80	0.78	0.78
HF	Men	0.82	0.81	0.80	0.79	0.79
	Women	0.82	0.82	0.81	0.80	0.79
CV mortality	Men	0.81	0.80	0.78	0.77	0.77
	Women	0.81	0.81	0.80	0.78	0.78

There are a number of caveats to note regarding the above methodology of dose adjustment. Firstly, the pre-treatment blood pressure would, in theory, be lowered by the first drug and that should be taken into account when calculating the reduction in blood pressure from the second drug and beyond. However, the pre-treatment systolic BP has been taken to be 150 mmHg for 1, 2 and 3 drugs, and then the corresponding reduction in systolic BP was identified from Law 2009. In reality, if someone had to have more drugs added, then this must be because their blood pressure had not been controlled, in which case it is likely they were still hypertensive, so this was not felt to be an extreme assumption. Secondly, part of the Law method of working out the impact on relative risk from reduced blood pressure was that age-specific regression slopes were also identified thus enabling the reduction in disease events for any age. The age adjustments were not been incorporated into the dose adjustment of the Law data, as the committee felt that this was an excessive departure from the original Brunström data. This also explains why the relative risk reductions from Law table 3 themselves were not used to derive the relative decrease in risk ratio from more drugs, as this would have also included the age adjustments. While in practice the Law study is well respected, the results generated are hypothetical and therefore different to a real study that would involve following up with people to identify treatment effects.

The committee felt that this analysis would reflect more favourable treatment effects than the base-case data (particularly the older the person is), but not as favourable as the Law data.

1.2.4.6 SA3: Heart failure relative risk reduction of 1 (probabilistic)

The committee felt that because the way heart failure is diagnosed has changed over time, this is likely to have influenced the number of heart failure events identified in trials and therefore how effective treatment appears. The diagnosis of heart failure has evolved from being a purely clinical diagnosis to one that utilised biomarkers and echocardiography. As most trials investigating hypertension tend to be quite old, then newer trials are likely to find a difference in the number of events than the older trials, and we cannot be certain that the heart failure in the older trials was genuine. Therefore, to capture the uncertainty around heart failure events, the relative risk reduction in heart failure events from antihypertensive treatment was set to 1. This means there would be no difference in the number of heart failure events between those on treatment and no treatment.

Another issue that this sensitivity analysis could be interpreted as testing, was that there is some evidence that suggests antihypertensives have no effect on reducing particular types of heart failure like HF-PEF heart failure, which can make up around 50% of heart failure types.

Another way to interpret this sensitivity analysis is that the treatment effect will only apply to the events that make up the QRISK calculator, as this does not include heart failure anyway.

1.2.4.7 SA4: Using the lower confidence interval for base case treatment effect

Table 27: Lower confidence intervals of base case treatment effect

Outcome	Lower CI
CHD	0.76
Stroke	0.72
Heart failure	0.73
Cardiovascular mortality	0.65

1.2.4.8 SA5: Using upper confidence interval for base case treatment effect

Table 28: Upper confidence intervals of base case treatment effect

Outcome	Upper CI
CHD	0.96
Stroke	1.01
Heart failure	1.04
Cardiovascular mortality	1.14

Annual increase in risk for CV event

1.2.4.9 SA6: Assuming annual increase in CV risk for women is same as men

Sensitivity analysis around the annual risk increase for women was considered important because there tends to be under treatment of hypertension in women. The committee felt it was important to test whether the model was biased against treatment for women, as women have a lower annual in risk in the base case, so their risk increases slower over time resulting in a lower absolute benefit from treatment.

This analysis assumed that the risk increase for each year of age for women was the same as men of 0.03%.

1.2.4.10 SA7: Assuming annual increase in CV risk for women is halfway between the base case value for women and men

Assuming that the risk increase for each year of age for women was halfway between the base case values for women and men: 0.019%.

Costs

1.2.4.11 SA8: Drug costs lower by 50%

Table 29: Lower drug costs

		Men				Women			
Age	Treatment	1	2	3+	Average	1	2	3+	Average
35–44	No. drugs (%)	61%	31%	8%		62%	28%	11%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£6.58	£13.36	£20.14	£9.83	£6.58	£13.36	£20.14	£9.88
45–54	No. drugs (%)	53%	33%	14%		58%	32%	10%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£6.58	£13.36	£20.14	£10.74	£6.58	£13.36	£20.14	£10.08
55–64	No. drugs (%)	44%	38%	18%		51%	35%	13%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	

Age	Treatment	Men				Women			
		1	2	3+	Average	1	2	3+	Average
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£6.78	£13.36	£20.14	£11.68	£6.78	£13.36	£20.14	£10.87
65–74	No. drugs (%)	39%	39%	22%		44%	38%	18%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£6.78	£13.36	£20.14	£12.30	£6.78	£13.36	£20.14	£11.64
75+	No. drugs (%)	38%	40%	22%		41%	39%	20%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£6.78	£13.36	£20.14	£12.40	£6.78	£13.36	£20.14	£12.05

1 **1.2.4.12 SA9: Drug costs higher by 50%**

2 **Table 30: Higher drug costs**

Age	Treatment	Men				Women			
		1	2	3+	Average	1	2	3+	Average
35–44	No. drugs (%)	61%	31%	8%		62%	28%	11%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£19.75	£40.08	£60.42	£29.49	£19.75	£40.08	£60.42	£29.65
45–54	No. drugs (%)	53%	33%	14%		58%	32%	10%	
	A†	100%	100%	100%		100%	100%	100%	
	C†	0%	50%	100%		0%	50%	100%	
	D†	0%	50%	100%		0%	50%	100%	
	Average cost/person	£19.75	£40.08	£60.42	£32.23	£19.75	£40.08	£60.42	£30.23
55–64	No. drugs (%)	44%	38%	18%		51%	35%	13%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£20.34	£40.08	£60.42	£35.03	£20.34	£40.08	£60.42	£32.60
65–74	No. drugs (%)	39%	39%	22%		44%	38%	18%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	

Age	Treatment	Men				Women			
		1	2	3+	Average	1	2	3+	Average
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£20.34	£40.08	£60.42	£36.89	£20.34	£40.08	£60.42	£34.92
75+	No. drugs (%)	38%	40%	22%		41%	39%	20%	
	A†	0%	100%	100%		0%	100%	100%	
	C†	50%	50%	100%		50%	50%	100%	
	D†	50%	50%	100%		50%	50%	100%	
	Average cost/person	£20.34	£40.08	£60.42	£37.19	£20.34	£40.08	£60.42	£36.16

1.2.4.13 SA10: Health state costs halved

See Table 31.

1.2.4.14 SA11: Health state costs doubled

Table 31: Upper and lower bounds of health state costs tested

State	Costs half of base case value (annual)	Costs double of base case value (annual)
Stroke	£11,538	£46,151
Post-stroke	£2,591	£10,366
TIA	£873	£3,492
Post-TIA	£293	£1,173
Myocardial infarction	£2,321	£9,282
Post-MI	£384	£1,536
Stable angina	£454	£1,816
Post-stable angina	£137	£547
Unstable angina	£1,168	£4,672
Post-unstable angina	£137	£547
Heart failure	£1,360	£5,438
Post-heart failure	£353	£1,411

Resource use

1.2.4.15 SA12: Nurse undertaking appointments instead of GP

A nurse appointment costs £10.85. This is based on the cost per hour of GP nurse time of £42 from PSSRU 2017,[12] and the duration of contact being 15.5 minutes taken from the PSSRU 2015[11] (as the duration of contact was not included in later versions). A GP consultation costs £38 per person contact lasting 9.22 minutes, so nurse time has a lower cost.

1.2.4.16 SA13: Number of consultations in first year doubled

The number of consultations in the first year for people on treatment will be doubled in a sensitivity analysis (see Table 32).

Table 32: Number of consultations in first year for people on treatment

	Number of consultations		
	On 1 drug	On 2 drugs	On 3 drugs
Base case	2	3	4
SA	4	6	8

Adverse events

1.2.4.17 SA14: Assuming no adverse events from treatment

1.2.4.18 SA15: Using longer length of stay following a fall

A longer length of stay of 8.6 days was used in a sensitivity analysis. This is based on data that a committee member provided from Taunton and Somerset NHS foundation trust that identified an average length of stay of 8.6 days for those aged over 65 years admitted following a fall.

1.2.4.19 SA16: Applying over 75s risk of AKI to falls

In the base case, the ratio of AKI events for those over 75 years compared to under 75 years was found to be 2.29.[45] This risk increase for those over 75 years was also applied to falls in this sensitivity analysis.

1.2.4.20 SA17: Applying fall utility loss for 4 months

The utility loss associated with a fall was based on a source that measured the utility loss from a hip fracture at 4 months.[44] As not to overestimate the impact of adverse events in the base case, the utility loss was only applied for 4 weeks based on committee estimate of recovery after a fall. However, in this sensitivity analysis, the utility loss was applied for 4 months, as that was the duration that it was measured at in the study.

Utilities

1.2.4.21 SA18: Lower confidence interval

Table 33: Lower and upper bounds of utility values

State	Lower confidence interval	Upper confidence interval
Stable angina	0.73	0.88
Post-stable angina	0.73	0.88
Unstable angina	0.70	0.84
Post-unstable angina	0.84	0.92
MI	0.72	0.80
Post-MI	0.84	0.92
TIA	0.85	0.95
Post-TIA	0.85	0.95
Stroke	0.55	0.71
Post-stroke	0.55	0.71
Heart failure	0.64	0.72
Post-heart failure	0.64	0.72

1.2.4.22 SA19: Upper confidence interval

See Table 33.

Mortality

1.2.4.23 SA20: Doubling the SMR associated with heart failure

In the base case, it was decided that a lower SMR would be a more conservative assumption. However, in a sensitivity analysis the heart failure SMR was doubled from 2.2 to 4.4 to see what impact this would have. This was based on committee opinion.

1.2.5 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross-referencing the cohorts age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the number of years after entry to the model.

People start in cycle 0 in the 'No CVD event' health state. People moved to the dead health state at the end of each cycle as defined by the mortality transition probabilities, and to other health states dependent on probabilities of developing CV disease. Transition probabilities to CV first event states vary by risk subgroup, age, sex, time in the model and whether on treatment or not. Non-CV mortality transition probabilities from the well state and post-CV event mortality transition probabilities vary depending on age, sex, and health state. See sections 1.2.3.3 for details about transition probabilities and treatment effects.

People aged over 60 and on treatment were at risk of adverse events. This is all alive people aged over 60 in the treatment arm of the model and those who have experienced a CV event, are alive and aged over 60 in the no treatment arm of the model (as it is assumed these people will start treatment).

Quality-adjusted life-years (QALY) were applied a half cycle correction, to reflect the assumption that people will transition between states on average halfway through a cycle. QALYs lost due to adverse events were subtracted from this. Adverse events for each cycle were calculated by applying the adverse event probabilities to the total time alive (taking into account half-cycle correction) on treatment each cycle to the cohort aged over 60 years. Total QALYs lost from adverse events were calculated by multiplying this by the QALY loss per adverse event. QALYs were discounted to reflect time preference (discount rate = 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs-per-cycle were calculated in the same way as QALYs. Higher monitoring and appointment costs were applied to all individuals undergoing treatment in their first year of treatment. Lower costs were applied to all subsequent years. Adverse events costs were added by multiplying the number of adverse events by the cost per adverse event.

Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:
r=discount rate per annum
n=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and costs accrued by each subgroup (of risk broken down into age and sex) was recorded. The total cost and

QALYs accrued by the cohort was divided by the number of people in the population to calculate a cost per person and cost per QALY.

1.2.6 Model validation

The model was developed in consultation with the committee; the model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis. This included inputting null and extreme values and checking that results were plausible given inputs. A second experienced health economist from the NGC peer reviewed the model; this included systematic checking of the model calculations.

1.2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher, the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost and then the options are ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated and ruled out if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

1.2.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[40] sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

1.3 Results

1.3.1 Base case

The base case results are for an age group of those aged 60 years. These results are from the probabilistic analysis based on 5,000 simulations. See Table 34.

Table 34: Base case results (per person, discounted)

	Undiscounted life-years	Total Costs	Total QALYs	ICER (£)	Prob Tx CE at £20k		Undiscounted life-years	Total Costs	Total QALYs	ICER (£)	Prob Tx CE at £20k
	Male						Female				
5% risk											
No Tx	23.66	£2,925	12.93		55%		26.16	£3,362	13.17		55%
Tx	23.79	£4,129	12.98	21,849	45%		26.30	£4,561	13.23	21,727	45%
10% risk											
No Tx	22.84	£4,187	12.52		16%		25.24	£5,258	12.73		14%
Tx	23.03	£5,192	12.61	10,676	84%		25.46	£6,180	12.83	9,399	86%
15% risk											
No Tx	22.09	£5,366	12.14		7%		24.41	£7,016	12.33		5%
Tx	22.34	£6,194	12.26	6,491	93%		24.69	£7,700	12.46	5,103	95%
20% risk											
No Tx	21.40	£6,465	11.77		3%		23.67	£8,637	11.95		3%
Tx	21.70	£7,148	11.93	4,396	97%		23.98	£9,120	12.11	3,024	97%

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

Table 35: Base case incremental results (per person, discounted)

Risk	Incremental Costs	Incremental QALYs	ICER	Risk threshold analysis	Incremental Costs	Incremental QALYs	ICER	Risk threshold analysis
	Male				Female			
5%	£1,204	0.06	£21,849		£1,200	0.06	£21,727	
10%	£1,005	0.09	£10,676		£922	0.10	£9,399	
15%	£828	0.13	£6,491		£684	0.13	£5,103	
20%	£683	0.16	£4,396		£483	0.16	£3,024	
				5.39%				**5.27%**

Note that values shaded red are above the NICE cost effectiveness threshold of £20,000 per QALY.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years.

In all risk subgroups, treatment was associated with higher costs and QALYs than no treatment. The results showed that treatment was not cost-effective for the 5% risk subgroup for either men or women, but was cost-effective for the 10% risk and higher subgroups. The ICER for treatment at 5% risk was only slightly above the £20,000 threshold and there is high uncertainty in the conclusion, with no treatment being cost-effective for men in 55% of iterations. A threshold analysis to identify the risk level at which treatment becomes cost effective (at £20,000 per QALY) for this age group showed this is slightly higher than 5% for both men and women (Table 35).

Note that the threshold risk level was based on the deterministic results, not the probabilistic results, although the results are similar. According to Table 19, the risk thresholds identified were below the minimum risk level of someone aged 60 years with stage 1 hypertension even if they were at their healthiest. This implies that effectively it was cost-effective to treat all those aged 60 years with stage 1 hypertension regardless of risk level. Because of the

uncertainty around the cost-effectiveness of treatment at lower risk levels for women in particular, the minimum risk level from Table 19 (of 5.3%) was very close to the risk threshold identified from the model. This tells us that there is more uncertainty associated with the cost-effectiveness of treatment in lower risk women.

The incremental cost decreased and incremental QALY increased, as the risk subgroup increased. The cost decreased as risk increased because there were more events being avoided at higher risk levels and therefore there were greater savings from events avoided to offset the treatment and adverse events costs. Whereas at lower levels of risk, such as 5%, the events avoided were fewer; therefore, the savings from treatment did not offset the treatment and adverse event costs as much. Likewise with quality of life: the more events avoided, the larger the quality of life difference between treatment and no treatment. In summary: as would be expected, the same treatment effect had a larger absolute impact on events when there was a higher baseline risk.

The breakdown of number of events per 1,000 can be seen below in Table 36.

Table 36: Base case results - Breakdown of events per 1,000

	SA	UA	MI	TIA	STr	HF	Total CV events
Male							
5% risk							
No treatment	51	18	38	16	68	55	246
Treatment	46	17	35	15	64	54	230
10% risk							
No treatment	75	25	53	23	90	70	336
Treatment	68	23	48	22	85	68	314
15% risk							
No treatment	97	31	66	30	109	82	414
Treatment	88	29	61	28	103	80	388
20% risk							
No treatment	116	36	78	37	124	91	482
Treatment	106	33	72	34	119	89	453
Female							
5% risk							
No treatment	38	9	19	17	78	41	202
Treatment	34	8	17	16	72	38	184
10% risk							
No treatment	64	14	29	26	116	58	309
Treatment	57	13	27	24	108	55	284
15% risk							
No treatment	88	19	38	35	148	73	401
Treatment	79	17	35	32	138	69	371
20% risk							
No treatment	110	24	46	42	174	85	481
Treatment	99	22	42	39	164	81	447

Abbreviations: SA: Stable angina; UA: Unstable angina; MI: Myocardial infarction; TIA: Transient ischaemic attack; ST: Stroke; HF: Heart failure; CV: cardiovascular.

The distribution of events for both sexes aged 60 years were weighted towards stable angina and stroke. Hence, at higher risk levels the number of these events increased at a faster rate.

The breakdown of costs can be seen in Table 37.

Table 37: Base case results - cost breakdown

	Drug/ monitoring costs	Adverse event costs	SA costs	UA costs	MI costs	TIA costs	STr costs	HF costs	Total CV event costs
Male									
5% risk									
No treatment	£661	£27	£84	£39	£185	£63	£1,700	£165	£2,236
Treatment	£1,628	£440	£75	£35	£166	£57	£1,571	£157	£2,061
10% risk									
No treatment	£686	£44	£145	£61	£298	£105	£2,604	£244	£3,457
Treatment	£1,594	£428	£129	£55	£267	£95	£2,394	£230	£3,170
15% risk									
No treatment	£710	£60	£204	£81	£405	£146	£3,445	£316	£4,596
Treatment	£1,561	£418	£181	£73	£364	£132	£3,167	£297	£4,215
20% risk									
No treatment	£734	£75	£261	£100	£505	£185	£4,225	£382	£5,657
Treatment	£1,531	£408	£232	£90	£455	£168	£3,904	£360	£5,209
Female									
5% risk									
No treatment	£700	£27	£83	£25	£104	£66	£2,215	£141	£2,634
Treatment	£1,709	£475	£72	£22	£92	£59	£2,002	£130	£2,378
10% risk									
No treatment	£732	£48	£154	£46	£180	£117	£3,749	£231	£4,478
Treatment	£1,674	£464	£135	£41	£160	£105	£3,388	£213	£4,042
15% risk									
No treatment	£762	£68	£223	£67	£252	£166	£5,166	£313	£6,186
Treatment	£1,641	£453	£197	£59	£225	£149	£4,686	£290	£5,606
20% risk									
No treatment	£792	£86	£290	£86	£317	£211	£6,468	£387	£7,759
Treatment	£1,610	£443	£257	£77	£285	£190	£5,898	£360	£7,067

Abbreviations: SA: Stable angina; UA: Unstable angina; MI: Myocardial infarction; TIA: Transient ischaemic attack; STr: Stroke; HF: Heart failure; CV: cardiovascular.

The cost of stroke was very high in the model, and stroke for this age group was also one of the most common events based on the distribution of first events; therefore, the cost of stroke was a large contributor to the overall cost. The higher incremental cost between treatment and no treatment was mostly driven by the difference in drug and monitoring and adverse event costs.

For women the treatment costs are being offset more by the savings from events avoided because women have a higher risk of stroke than other events compared to men.

Differential treatment duration

As previously discussed in section 1.2.2.2, a limitation of the model was that people cannot exit from stage 1 hypertension to become eligible for treatment because of other reasons (unless they have a CV event). This was a simplification of the model but one that seemed reasonable, as modelling underlying characteristics such as blood pressure increases over time, change in characteristics that could increase CV risk, and the risk of developing other comorbid conditions, was felt to be too complex. An exploratory sensitivity analysis was undertaken to see whether the results, based on the current model structure (that does not allow people to exit stage 1 hypertension), would be impacted by addressing the simplification. This sensitivity analysis involved making assumptions about the differential treatment duration, in other words, testing arbitrary time points at which people would become eligible for treatment in the no treatment arm. This exploratory sensitivity analysis was essentially a way to test the effect of shorter durations of treatment and whether that affected the results.

For the base-case cohort of those aged 60 years, the time points tested at which those on no treatment would hypothetically become eligible for treatment were after year 1, year 5, and year 10. The results of these analyses are shown below in Table 38 in terms of the risk thresholds at which treatment becomes cost-effective. The results of the base case are also shown for comparison, as well as the minimum risk levels for this age group.

Table 38: Differential treatment duration analysis, age 60

Years before meeting other criteria for treatment	Risk threshold	
	Male	Female
1	*6.5%*	*5.0%*
5	*5.8%*	*4.9%*
10	*5.1%*	*4.7%*
Never (base case) (b)	***5.4%***	***5.3%***
Minimum risk level (a)	***8.5%***	***5.3%***

The cells in orange indicate that the risk thresholds are below the minimum risk level, that is, below the values in orange text. If this is the case, then this means that it is cost effective to treat all at that age and sex.
(a) See Table 19 for information on the minimum risk levels and how they are calculated.
(b) Although note that those that have CV events can go onto treatment in the model.

The results were similar across different differential treatment durations tested. As the risk thresholds for all differential treatment durations were lower than the minimum risk levels of someone age 60 years (either male or female) with stage 1 hypertension, this means that it was cost effective to treat all with stage 1 hypertension aged 60 years, regardless of how soon they may become eligible for antihypertensive treatment due to other reasons.

Note: It might be expected that the risk level, at which treatment is cost-effective, would reduce as the differential treatment duration increases because the CV risk was at its lowest in the first year. Therefore, there would be a lower absolute benefit from treatment for a certain treatment cost. When the duration of no treatment increased and as risk also increased over time, the absolute benefit from treatment would be higher and the benefit would rise at a faster rate than the costs. Higher treatment benefit also meant more events avoided and more costs saved to offset against the treatment costs (which do not change substantially over time). However, as can be seen from Table 38, this was not the case in the analysis with the longest differential treatment duration (the base case), as this did not have the lowest risk threshold. This was because many of the inputs in the model change as people age, such as non-CV mortality increasing with age, the distribution of events changing with age (although not always increasing with age, as the risk of some events falls with age or peaks at age 60 and then decreases again), drug costs increase with age, and utilities decrease with age. In the model, a test was undertaken where anything that increased with age was set to be the same for all age groups, so as not to vary with age.

This led to a decreasing pattern of risk thresholds (with the base case having the smallest risk threshold), as expected.

1.3.2 Sensitivity analyses

1.3.2.1 Results from other age groups (probabilistic)

Results for the sensitivity analyses where the cohort age was changed from the base case age of 60 years are summarised in Table 39. The results for the age 60 years group are also included for comparison.

Table 39: Results for other age subgroups

Risk	Incremental Costs	Incremental QALYs	ICER	Probability Tx CE at 20k	Incremental Costs	Incremental QALYs	ICER	Probability Tx CE at 20k
	Male				Female			
Age 60 (base case)								
5%	*£1,204*	*0.06*	*£21,849*	*45%*	*£1,200*	*0.06*	*£21,727*	*45%*
10%	*£1,005*	*0.09*	*£10,676*	*84%*	*£922*	*0.10*	*£9,399*	*86%*
15%	*£828*	*0.13*	*£6,491*	*93%*	*£684*	*0.13*	*£5,103*	*95%*
20%	*£683*	*0.16*	*£4,396*	*97%*	*£483*	*0.16*	*£3,024*	*97%*
Age 40								
5%	£955	0.13	£7,614	93%	£878	0.11	£7,774	94%
10%	£661	0.18	£3,664	99%	£415	0.18	£2,290	99%
15%	£431	0.22	£1,928	99%	£25	0.23	£108	100%
20%	£218	0.25	£856	100%	-£301	0.27	Dominant	100%
Age 50								
5%	£1,073	0.09	£11,372	83%	£1,049	0.08	£12,362	80%
10%	£826	0.15	£5,629	97%	£683	0.14	£4,853	97%
15%	£620	0.19	£3,257	99%	£366	0.19	£1,976	99%
20%	£425	0.22	£1,921	100%	£108	0.22	£494	99%
Age 70								
5%	£1,052	0.02	£44,094	6%	£1,067	0.03	£34,661	16%
10%	£924	0.04	£21,071	48%	£889	0.06	£15,634	64%
15%	£815	0.06	£13,021	72%	£721	0.08	£8,901	82%
20%	£715	0.08	£9,276	81%	£577	0.10	£5,774	88%
Age 75								
5%	£935	0.02	£57,286	0%	£964	0.02	£41,845	5%
10%	£832	0.03	£24,834	36%	£807	0.05	£17,458	59%
15%	£745	0.05	£15,527	64%	£674	0.07	£10,272	80%
20%	£656	0.06	£10,850	77%	£542	0.08	£6,462	87%

Note that cells shaded red are above the NICE cost effectiveness threshold of £20,000 per QALY. Cells shaded green mean treatment is a dominant intervention.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years, Tx = treatment.

The same pattern as the base case emerged in terms of smaller incremental costs and higher incremental QALYs as risk increased for each age group, leading to smaller ICERs for the higher risk groups.

In the age 40 and 50 years analyses, it was more likely that the lower risk subgroups were cost-effective. This was because younger people live longer and accrue more life-years overall; therefore, they had more time to be at risk of events. The events avoided from treatment therefore led to larger QALY gains.

Table 40 gives a summary of the risk thresholds, above which treatment is cost-effective, for all age groups. These were also compared to the minimum risk level for someone of that age and sex to allow the interpretation in the final column of the table, which identified how the decision to treat would be interpreted in practice based on the model's results. There are only 2 subgroups for which the risk threshold the model predicted was above the minimum risk levels, which were women aged 40 and 50 years. However, in general, the risk thresholds were pretty close to the feasible risk levels, and the majority of people were probably not likely to be perfectly healthy except for stage 1 hypertension, implying that on balance for the whole stage 1 population, it may be cost-effective to treat regardless of risk.

Table 40: Summary of risk thresholds for all age groups

Age	1) Minimum risk level from QRISK2	2) Risk threshold at which treatment becomes cost effective (from model)	Decision in clinical practice (a)
Male			
40	1.50%	0.83%	Treat all
50	4.00%	2.12%	Treat all
60	8.50%	5.39%	Treat all
70	16.40%	10.33%	Treat all
75	22%	12.07%	Treat all
Female			
40	0.90%	1.86%	Treat above 1.86% risk
50	2.30%	3.06%	Treat above 3.06% risk
60	5.30%	5.27%	Treat all
70	11.70%	7.99%	Treat all
75	17.00%	8.99%	Treat all

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

Overall, in the older the age group, the bigger difference between the risk threshold that was cost-effective and the minimum CV risk level implies that those at the lower end of the distribution of risk in older people would be more comfortably above the threshold risk level.

The committee felt that numbers needed to treat (NNT) would also be a helpful way of interpreting the results, as this is a common way that clinicians explain the benefits of treatment to people. These were calculated by taking the crude average of the relative risk across all events for men and women in each age group, from Table 5, to derive an overall relative risk reduction in CV events from treatment for each age group and sex. These were then multiplied by the minimum risk levels from the QRISK2 (from Table 19) to derive absolute risk reductions. The reciprocal of these absolute risk reductions were the numbers needed to treat. These are 10-year numbers needed to treat because the minimum risk levels are based on 10-year predicted risks. The 10-year predicted QRISK2 risks were converted to 5-year risks to work out 5-year numbers needed to treat, because that is more

commonly used in practice. These should be interpreted as the number of people that have to be treated to avoid 1 cardiovascular event. These are presented in Table 41.

Table 41: 5 and 10 year numbers needed to treat

Age	Minimum risk level from QRISK2	absolute risk reduction	NNTs	Interpretation		
10 YEAR NNT'S						
Male						
40	1.50%	0.013	79	need to treat	79	men to avoid 1 event
50	4.00%	0.033	30	need to treat	30	men to avoid 1 event
60	8.50%	0.073	14	need to treat	14	men to avoid 1 event
70	16.40%	0.152	7	need to treat	7	men to avoid 1 event
75	22%	0.206	5	need to treat	5	men to avoid 1 event
Female						
40	0.90%	0.007	136	need to treat	136	women to avoid 1 event
50	2.30%	0.019	52	need to treat	52	women to avoid 1 event
60	5.30%	0.046	22	need to treat	22	women to avoid 1 event
70	11.70%	0.107	9	need to treat	9	women to avoid 1 event
75	17.00%	0.153	7	need to treat	7	women to avoid 1 event
5 YEAR NNT'S						
Male						
40	0.75%	0.006	157	need to treat	157	men to avoid 1 event
50	2.02%	0.017	59	need to treat	59	men to avoid 1 event
60	4.34%	0.037	27	need to treat	27	men to avoid 1 event
70	8.57%	0.079	13	need to treat	13	men to avoid 1 event
75	12%	0.109	9	need to treat	9	men to avoid 1 event
Female						
40	0.45%	0.004	271	need to treat	271	women to avoid 1 event
50	1.16%	0.010	104	need to treat	104	women to avoid 1 event
60	2.69%	0.023	43	need to treat	43	women to avoid 1 event
70	6.03%	0.055	18	need to treat	18	women to avoid 1 event
75	8.90%	0.080	12	need to treat	12	women to avoid 1 event

Differential treatment duration (probabilistic)

In Table 42, the results are presented for males and females and age subgroups from the differential treatment duration analyses.

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

Table 42: Differential treatment duration results for all ages

Years before meeting other criteria for treatment	Risk threshold				
	Age 40	Age 50	Age 60	Age 70	Age 75
MALES					
1	4.4%	4.3%	6.5%	11.1%	12.4%
5	3.7%	3.7%	5.8%	10.9%	12.1%
10	2.8%	2.9%	5.1%	-	-
20	1.3%	2.2%	-	-	-
Never (base case)	**0.8%**	**2.1%**	**5.4%**	**10.3%**	**12.1%**
Minimum risk level	***1.5%***	***4.0%***	***8.5%***	***16.4%***	***22.3%***
FEMALES					
1	2.7%	3.0%	5.0%	7.9%	8.5%
5	2.4%	2.8%	4.9%	8.0%	8.5%
10	2.1%	2.5%	4.7%	-	-
20	1.7%	2.8%	-	-	-
Never (base case)	**1.9%**	**3.1%**	**5.3%**	**8.0%**	**9.0%**
Minimum risk level	***0.9%***	***2.3%***	***5.3%***	***11.7%***	***17.0%***

The cells in orange indicate that the risk thresholds are below the minimum risk level, that is, below the values in orange text. If this is the case, then this means that it is cost effective to treat all of that age and sex.

For men, the assumptions made about differential treatment duration was impacting the base-case conclusion in younger people, as there was some uncertainty about whether it was cost-effective to treat everyone in these groups if they may become eligible for treatment from other reasons in a shorter time frame.

For women, the differential treatment durations did not impact the base case conclusions because it was still not cost effective to treat all younger women, regardless of the assumptions tested about treatment duration.

Overall, what we can infer from the differential treatment duration analyses is that if an individual is aged 60 or over, there is more certainty that treating all those with stage 1 hypertension would be cost-effective. But below the age of 60 years, there are some people for whom it would be cost-effective and some for whom it wouldn't. This depends on their current risk level (more so for females) and on how soon it might be perceived an individual is likely to develop other reasons that make them eligible for treatment.

1.3.2.2 SA1: Using relative risks from Law 2009 (probabilistic)

The relative risks from the Law paper were more favourable than those in the base-case analysis; therefore, it is expected that the results would find treatment more cost-effective. The results are shown below in Table 43.

Table 43: Using relative risks from Law 2009

Analysis	Risk	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k
		Male				Female			
Age 60	**5%**	£535	0.246	£2,174	100%	£468	0.213	£2,201	100%
	10%	£46	0.374	£124	100%	-£248	0.350	Dominant	100%

(base case age)	**15%**	-£382	0.482	Dominant	100%	-£860	0.464	Dominant	100%
	20%	-£755	0.575	Dominant	100%	-£1,381	0.558	Dominant	100%
Age 40	**5%**	-£43	0.404	Dominant	100%	-£175	0.319	Dominant	100%
	10%	-£648	0.548	Dominant	100%	-£1,190	0.489	Dominant	100%
	15%	-£1,151	0.660	Dominant	100%	-£2,026	0.622	Dominant	100%
	20%	-£1,571	0.746	Dominant	100%	-£2,705	0.721	Dominant	100%
Age 50	**5%**	£227	0.340	£666	100%	£154	0.271	£570	100%
	10%	-£311	0.480	Dominant	100%	-£697	0.425	Dominant	100%
	15%	-£764	0.595	Dominant	100%	-£1,412	0.549	Dominant	100%
	20%	-£1,144	0.686	Dominant	100%	-£1,994	0.645	Dominant	100%
Age 70	**5%**	£627	0.142	£4,432	100%	£547	0.144	£3,807	100%
	10%	£249	0.237	£1,050	100%	-£2	0.252	Dominant	100%
	15%	-£95	0.322	Dominant	100%	-£493	0.348	Dominant	100%
	20%	-£404	0.397	Dominant	100%	-£928	0.431	Dominant	100%
Age 75	**5%**	£643	0.096	£6,717	100%	£576	0.105	£5,465	100%
	10%	£321	0.175	£1,835	100%	£115	0.195	£591	100%
	15%	£23	0.246	£93	100%	-£307	0.275	Dominant	100%
	20%	-£251	0.312	Dominant	100%	-£687	0.348	Dominant	100%

Cells shaded green mean treatment is a dominant intervention.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years, Tx = treatment.

Table 43 shows that for all ages and sexes treatment was cost-effective even if someone had a risk of 5%. The biggest changes in the base case are those aged 60 years and over, where 5% was not cost-effective before but was now even in those aged 75 years.

Treatment is dominant for most subgroups because a more generous treatment effect means that treatment avoids more events than in the base case; therefore, the cost savings from reduced events in the treatment arm outweighed the additional treatment costs (the intervention, monitoring, and adverse event costs). There was also more certainty that treatment is cost-effective using these lower treatment effects.

This shows that the model was sensitive to the treatment effect.

1.3.2.3 SA2: Adjusted base-case treatment effects (Brunström) to take into account more medication (probabilistic)

In this sensitivity analysis, the base-case relative risks were adjusted to take into account that the meta-analysis they were taken from included studies that were mainly based on 1 drug whereas in practice the average level of antihypertensive treatment is based on more than 1 drug. These relative risks were seen as being slightly more favourable than the base case but not as favourable as the Law relative risks. The results can be seen in Table 44.

Table 44: Using adjusted Brunström relative risks taking into account more medication

Analysis	Risk	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k
		Male				**Female**			
	5%	£963	0.130	£7,385	94%	£965	0.110	£8,766	91%

Age 60 (base case age)	**10%**	£671	0.202	£3,328	99%	£539	0.185	£2,915	98%
	15%	£424	0.261	£1,622	99%	£215	0.243	£884	99%
	20%	£200	0.311	£643	99%	-£91	0.293	Dominant	100%
Age 40	**5%**	£734	0.197	£3,719	98%	£732	0.151	£4,859	96%
	10%	£416	0.265	£1,566	99%	£219	0.231	£946	99%
	15%	£139	0.318	£438	99%	-£185	£0	Dominant	100%
	20%	-£70	0.357	Dominant	99%	-£503	0.331	Dominant	99%
Age 50	**5%**	£834	0.172	£4,856	97%	£839	0.134	£6,272	94%
	10%	£533	0.245	£2,176	99%	£379	0.210	£1,806	99%
	15%	£279	0.301	£926	99%	£37	£0	£139	99%
	20%	£65	0.343	£190	100%	-£287	0.312	Dominant	100%
Age 70	**5%**	£868	0.080	£10,894	90%	£854	0.079	£10,795	87%
	10%	£627	0.136	£4,602	98%	£518	0.141	£3,666	98%
	15%	£408	0.188	£2,173	100%	£224	0.196	£1,144	99%
	20%	£221	0.231	£956	100%	-£34	0.242	Dominant	99%
Age 75	**5%**	£805	0.054	£14,792	79%	£808	0.058	£13,937	78%
	10%	£598	0.102	£5,860	98%	£525	0.109	£4,806	97%
	15%	£411	0.144	£2,856	99%	£273	0.155	£1,758	99%
	20%	£245	0.182	£1,346	100%	£47	0.195	£239	100%

Cells shaded green mean treatment is a dominant intervention.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years, Tx = treatment.

Similar to the previous analysis, treatment was cost-effective in all subgroups, even down to a 5% risk level for the oldest of age groups, confirming again that the model was sensitive to small changes in the treatment effect.

The biggest impact was on the older age groups of 70 and 75 years. In the base case, the 5% risk level for both men and women and the 10% risk level for men were above the £20,000 threshold. The ICERs have reduced substantially in those groups because in the base case, age adjustments were applied to the Brunström data so the relative risks for those aged 70 and 75 years were much higher, reflecting that the source of age adjustments (Law) found increasing relative risks for older ages. Whereas in this sensitivity analysis, the age adjustments were not applied because the committee felt that the data had already been adjusted for the number of drugs. Therefore, for the groups age 70 and 75 years, the relative risk used in this analysis was much lower than that used in the base case for those age groups.

1.3.2.4 SA3: Heart failure relative risk reduction of 1 (probabilistic)

This sensitivity analysis tested the uncertainty around treatment effect from trial data because the definitions of heart failure have changed over time and older trials might have overestimated the treatment effect on heart failure if, in fact, the heart failure identified in the trial wouldn't be classified as such anymore. Additionally, there is some evidence that suggests antihypertensive treatment has no effect on heart failure with preserved ejection fraction (HF-PEF). See Table 45 below for the results.

Table 45: Applying relative risk of 1 to heart failure

Analysis	Risk	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k	Incremental cost	Incremental QALYs	ICER	Probability Tx CE at 20k
		Male				Female			
Age 60 (base case age)	5%	£1,217	0.043	£28,032	28%	£1,211	0.046	£26,320	33%
	10%	£1,025	0.079	£12,984	75%	£934	0.084	£11,093	79%
	15%	£846	0.109	£7,783	89%	£700	0.116	£6,042	90%
	20%	£695	0.134	£5,177	94%	£492	0.141	£3,500	95%
Age 40	5%	£975	0.106	£9,157	89%	£901	0.100	£9,051	89%
	10%	£685	0.159	£4,303	97%	£438	0.163	£2,683	99%
	15%	£454	0.197	£2,299	99%	£61	£0	£290	100%
	20%	£249	0.228	£1,092	99%	-£252	0.248	Dominant	100%
Age 50	5%	£1,095	0.079	£13,888	73%	£1,061	0.073	£14,576	71%
	10%	£851	0.127	£6,694	94%	£700	0.125	£5,606	95%
	15%	£628	0.166	£3,789	98%	£385	£0	£2,297	98%
	20%	£443	0.198	£2,236	99%	£119	0.198	£600	99%
Age 70	5%	£1,058	0.018	£59,072	1%	£1,076	0.024	£45,075	7%
	10%	£937	0.035	£26,964	34%	£897	0.047	£19,141	53%
	15%	£826	0.050	£16,436	61%	£742	0.066	£11,287	73%
	20%	£733	0.063	£11,618	73%	£597	0.083	£7,175	83%
Age 75	5%	£941	0.012	£78,673	0%	£968	0.018	£53,516	2%
	10%	£842	0.026	£32,626	20%	£821	0.037	£22,433	44%
	15%	£751	0.038	£19,741	52%	£678	0.054	£12,581	72%
	20%	£659	0.050	£13,057	70%	£549	0.069	£7,984	82%

Note that cells shaded red are above the NICE cost effectiveness threshold of £20,000 per QALY. Cells shaded green mean treatment is a dominant intervention.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years, Tx = treatment.

Applying no reduction in relative risk for heart failure means that antihypertensive treatment did not have an effect on that event. Treatment was generally less cost-effective with all ICERs having increased because there were fewer cost savings and fewer QALYs to be gained, as heart failure was not avoided due to antihypertensive treatment anymore. The group most affected were women aged 75 years, where in the base case 10% risk was cost-effective, but now it is not.

Another reason the ICERs have increased is an anomalous one because there were actually more heart failure events in the treatment arm, as there were more people in the 'no CVD event' state. Therefore, more people were at risk of heart failure. This is partly due to the fact that people could not have repeat events in the model. Thus, a higher risk of heart failure due to having had a previous CV event was not captured, which would lead to more heart failures in the no treatment arm because more people were having first CV events.

1.3.2.5 Other sensitivity analyses

The results of all other sensitivity analyses described in Section 1.2.4 are summarised in Table 46 below. These analyses were run deterministically for the base-case age group of age 60 years. The base-case results presented in the table below for reference are also the

1 deterministic results, hence a slight difference to the base-case results presented in Table 35
2 due to the uncertainty around the inputs in the probabilistic analysis.

3 **Table 46: Sensitivity analysis results**

Analysis	Risk	Incremental cost	Incremental QALYs	ICER	Incremental cost	Incremental QALYs	ICER
		Male			Female		
Base case	***5%***	*£1,202*	*0.06*	*£21,441*	*£1,195*	*0.06*	*£21,163*
	10%	*£1,004*	*0.10*	*£10,569*	*£920*	*0.10*	*£9,321*
	15%	*£830*	*0.13*	*£6,488*	*£684*	*0.13*	*£5,135*
	20%	*£676*	*0.16*	*£4,356*	*£482*	*0.16*	*£2,998*
SA4: Lower CI of Base case treatment effect	**5%**	£910	0.16	£5,686	£844	0.15	£5,755
	10%	£585	0.25	£2,354	£359	0.24	£1,475
	15%	£303	0.32	£936	-£52	0.32	Dominant
	20%	£61	0.39	£158	-£397	0.39	Dominant
SA5: Upper CI of Base case treatment effect	**5%**	£1,497	-0.06	Dominated	£1,558	-0.05	Dominated
	10%	£1,422	-0.08	Dominated	£1,488	-0.06	Dominated
	15%	£1,345	-0.09	Dominated	£1,414	-0.08	Dominated
	20%	£1,266	-0.10	Dominated	£1,337	-0.09	Dominated
SA6: Annual CV risk increase for women the same as men	**5%**	£1,202	0.06	£21,441	£1,083	0.07	£15,437
	10%	£1,004	0.10	£10,569	£846	0.11	£8,001
	15%	£830	0.13	£6,488	£639	0.13	£4,735
	20%	£676	0.16	£4,356	£460	0.16	£2,902
SA7: Annual CV risk increase for women halfway between women and men	**5%**	£1,202	0.06	£21,441	£1,133	0.06	£17,618
	10%	£1,004	0.10	£10,569	£878	0.10	£8,539
	15%	£830	0.13	£6,488	£658	0.13	£4,895
	20%	£676	0.16	£4,356	£469	0.16	£2,934
SA8: Lower drug costs by 50%	**5%**	£1,023	0.06	£18,248	£1,013	0.06	£17,938
	10%	£837	0.10	£8,803	£750	0.10	£7,602
	15%	£673	0.13	£5,260	£526	0.13	£3,949
	20%	£529	0.16	£3,409	£335	0.16	£2,084
SA9: Increase drug costs by 50%	**5%**	£1,381	0.06	£24,635	£1,377	0.06	£24,387
	10%	£1,172	0.10	£12,334	£1,090	0.10	£11,040
	15%	£987	0.13	£7,716	£841	0.13	£6,320
	20%	£823	0.16	£5,302	£628	0.16	£3,912
SA10: Half health state costs	**5%**	£1,291	0.06	£23,025	£1,326	0.06	£23,478
	10%	£1,148	0.10	£12,084	£1,139	0.10	£11,535
	15%	£1,020	0.13	£7,973	£973	0.13	£7,312
	20%	£903	0.16	£5,822	£828	0.16	£5,157
SA11: Double health state costs	**5%**	£1,024	0.06	£18,274	£934	0.06	£16,532
	10%	£716	0.10	£7,538	£483	0.10	£4,892
	15%	£450	0.13	£3,518	£104	0.13	£780

	20%	£221	0.16	£1,424	-£212	0.16	Dominant
SA12: Nurse doing appointment instead of GP	**5%**	£828	0.06	£14,763	£798	0.06	£14,127
	10%	£652	0.10	£6,865	£548	0.10	£5,556
	15%	£499	0.13	£3,904	£336	0.13	£2,526
	20%	£366	0.16	£2,358	£157	0.16	£980
SA13: No. of consultations for first yr on treatment being doubled	**5%**	£1,291	0.06	£23,034	£1,283	0.06	£22,712
	10%	£1,087	0.10	£11,436	£1,000	0.10	£10,132
	15%	£906	0.13	£7,084	£757	0.13	£5,685
	20%	£746	0.16	£4,810	£549	0.16	£3,417
SA14: Having no adverse events	**5%**	£789	0.06	£12,968	£747	0.06	£12,115
	10%	£619	0.10	£6,225	£505	0.10	£4,875
	15%	£471	0.13	£3,567	£299	0.14	£2,171
	20%	£342	0.16	£2,151	£125	0.16	£760
SA15: Longer length of stay for falls	**5%**	£1,677	0.06	£29,913	£1,704	0.06	£30,178
	10%	£1,450	0.10	£15,258	£1,395	0.10	£14,137
	15%	£1,247	0.13	£9,754	£1,127	0.13	£8,465
	20%	£1,067	0.16	£6,876	£895	0.16	£5,571
SA16: Apply over 75s AKI risk to falls also	**5%**	£1,300	0.05	£23,653	£1,315	0.06	£23,849
	10%	£1,090	0.09	£11,589	£1,024	0.10	£10,504
	15%	£904	0.13	£7,119	£774	0.13	£5,859
	20%	£741	0.15	£4,794	£560	0.16	£3,503
SA17: Apply fall utility loss for 4 months	**5%**	£1,202	0.05	£25,644	£1,195	0.05	£25,633
	10%	£1,004	0.09	£11,623	£920	0.09	£10,278
	15%	£830	0.12	£6,926	£684	0.12	£5,488
	20%	£676	0.15	£4,579	£482	0.15	£3,155
SA18: Utilities lower CI	**5%**	£1,202	0.06	£20,004	£1,195	0.06	£19,511
	10%	£1,004	0.10	£9,845	£920	0.11	£8,581
	15%	£830	0.14	£6,035	£684	0.14	£4,717
	20%	£676	0.17	£4,046	£482	0.18	£2,749
SA19: Utilities upper CI	**5%**	£1,202	0.05	£23,101	£1,195	0.05	£23,121
	10%	£1,004	0.09	£11,407	£920	0.09	£10,201
	15%	£830	0.12	£7,014	£684	0.12	£5,633
	20%	£676	0.14	£4,717	£482	0.15	£3,298
SA20: Double SMR for HF	**5%**	£1,204	0.06	£20,952	£1,198	0.06	£20,647
	10%	£1,008	0.10	£10,356	£924	0.10	£9,135
	15%	£834	0.13	£6,376	£688	0.14	£5,054
	20%	£681	0.16	£4,294	£487	0.16	£2,968

Note that cells shaded red are above the NICE cost effectiveness threshold of £20,000 per QALY. Cells shaded green mean treatment is a dominant intervention.
Abbreviations: CE = cost effective, 20k = £20,000, ICER = incremental cost effectiveness ratio, QALYS = quality adjusted life-years.

Varying the base-case treatment effect to its lower bound (SA4) to test the maximum treatment effect reduced the ICERs, so much so that it became cost-effective to treat the 5% risk subgroup. For women, this made treatment in some of the higher risk subgroups

dominant, as the savings from events avoided outweighed the cost of treatment. For women in general, the higher risk subgroups had more favourable results than men (that is, lower ICERS or more likely to be dominant) because women were more at risk of the higher cost events such as stroke, compared to men, in terms of the distribution of events (Table 3).

Using the upper bound of the base-case treatment effect (SA5) to test the minimum treatment effect has the opposite effect in terms of treatment being a dominated intervention for all risk subgroups in both sexes. This is because for the outcomes of stroke, HF and CV mortality, the relative risk was actually above 1 for the upper confidence interval, meaning there were more events if a person is on treatment rather than fewer. Therefore, the results make sense that treatment would on balance be both costlier and less effective in terms of QALYs. Although it may not be considered realistic that treatment leads to more CV events, these results reflect the uncertainty within the data and the reality is that the true treatment effect is unknown.

Increasing the annual CV risk increase for women to halfway between the base case value for women and men (SA7), and to the same as the risk increase for men (SA6), reduced the ICERs for women, making treatment at 5% also cost-effective. This was as expected because the higher the annual increase in risk, the more events people have when not on treatment; therefore, the more events avoided from being on treatment, favouring treatment even more. This was considered an important sensitivity analysis for the committee for a number of reasons. For example, there is systematic under treatment in women, so the committee felt it was important to test whether the model was biasing against treatment against women, as women have a lower annual in risk in the base case, which means the slope of their risk increase over time is lower so they get lower absolute benefit from treatment. Additionally, some data suggests that cardiovascular risk increases at a faster rate in post-menopausal women, so testing higher annual risk increase overall could be one way to capture that. Finally, on a population level, the average woman is at lower CV risk than the average man, but as we were focusing on people with stage 1 hypertension (who have a higher risk by definition), then the risk profile of women may not behave in the same way as the average woman.

Reducing drug costs by 50% (SA8) makes treating at 5% risk cost-effective for both men and women compared to the base case, because it lowered the incremental costs, as it meant the drug costs were now more easily offset by the savings from reduced CV events. Higher drug costs (SA9) had the opposite effect, raising the ICERS slightly, but the risk level at which it was cost-effective to treat was still between 5 and 10%. Lowering health state costs (SA10) also raised the ICERs somewhat because events avoided led to smaller savings. Doubling health state costs (SA11) made treating at 5% cost-effective for men and women.

Other resource use varied include nurses undertaking monitoring appointments instead of GPs (SA12). This led to the 5% risk group being cost-effective to treat for both sexes now, as monitoring costs have reduced. Doubling the number of consultations in the first year of treatment (SA13) increased the ICERS slightly.

Having no adverse events in the model (SA14) had quite a large impact on the ICERS, reducing them by almost half. This is because having no adverse events meant there was no utility loss from the adverse events, thereby increasing the incremental QALY slightly compared to the base case. It also reduced the incremental costs by quite a lot, as although adverse events only applied to small proportion of people, the risk was applied every cycle to all those alive and on treatment, which added up. Having a longer length of stay for falls (SA15) increased the ICERS because it increased the adverse event cost associated with being on treatment. Applying a higher risk of a fall to those over 75 (SA16), and applying a longer utility loss for falls (SA17) also increased the ICERs. Although the risk level at which treatment was cost-effective was still between 5 and 10%.

Lowering the utilities associated with CV events (SA18) made treatment cost effective at 5%, as it made the health consequences associated with CV events more severe. Having higher utilities associated with CV events (SA19) slightly increased the ICERs.

Doubling the HF SMR had a minimal effect on the results.

Overall, the inputs that led to the biggest change in the results were the treatment effect, the annual increase in CV risk for women, the costs, and the adverse events.

1.4 Discussion

1.4.1 Summary of results

The base-case results show that, taking into consideration what the lowest CV risk level might be for someone who has stage 1 hypertension but is otherwise healthy, it was cost-effective to treat all men and women aged 60 or over.

The analysis on differential treatment duration for the base-case age group showed it remained cost-effective to treat all those aged 60 years with stage 1 hypertension, regardless of the assumptions tested about differential treatment duration. In other words, the conclusions did not change.

In the sensitivity analyses where the cohort age was varied (60 years was used in the base case) the results were similar. There were only a few exceptions, in the younger women (aged 40 years and borderline for aged 50 years), where the risk threshold that it was cost-effective to treat at was higher than the minimum risk level for that age and sex calculated using QRISK2. This meant that there would be females of these age groups of low-risk who it might not be cost-effective to treat.

The analyses on differential treatment duration for other age groups showed that in younger men the assumptions made about differential treatment duration did change the base-case results. The cost effectiveness of treatment for younger men depended on whether they would become eligible for antihypertensive treatment for alternative indications within around 20 years. For women, the assumptions tested about differential treatment duration did not affect the results, as it was still not cost-effective to treat all younger women (for example, the risk threshold remained at between 2.8–3.1% for women aged 50 years, which is above the lowest risk level for that group of 2.3%) regardless of the durations tested.

Testing various inputs in the model showed that the model is sensitive to treatment effect and that CV risk increased assumptions, costs, and adverse events. Overall, most inputs tested changed the magnitude of the ICERs but not necessarily the overall conclusions.

1.4.2 Limitations and interpretation

The aim of the model was to identify the risk level at which it was cost-effective to initiate treatment in people with stage 1 hypertension without target organ damage, established CVD, renal disease or diabetes.

One limitation was the structural assumption that people on no treatment will remain on no treatment their entire lives, unless they had a CV event. It is acknowledged that this was a simplification, as in reality people may become eligible for treatment for a variety of other reasons such as progressing to stage 2 hypertension. This may mean that the differential treatment duration within the model (that is, the period during which treatment costs and risks of CV events will vary between the 2 arms) in the base-case analysis was longer than in reality. It was felt too complex to model underlying characteristics like blood pressure and CV risk over time. However, this was explored through a sensitivity analysis that aimed to explore whether conclusions changed if there were shorter differential treatment durations.

As described above, this analysis found that the conclusions from the base-case analysis (cohort aged 60 years) were not changed, and it was cost-effective to treat all people irrespective of risk (once minimum possible risk had been taken into consideration). When this sensitivity analysis was combined with the sensitivity analysis varying the cohort starting age, the conclusions changed, such that for men aged 40 and 50 years it was no longer cost-effective to treat some people at very low-risk, but it did not change the conclusions for any age group in women. As we do not have data about the average time it takes for people with stage 1 hypertension (without target organ damage, established CV, renal disease or diabetes) to progress to starting treatment, it was not possible to specify what the most appropriate assumption is regarding differential treatment duration. This therefore suggests that there is some uncertainty about treating very low-risk people related to this limitation.

The model was considered conservative in many ways. Only 1 CV event was modelled and repeat events were not considered. This is conservative because the risk of other CV events increased in people who have already had an event. Therefore, if treatment avoids the first event, then it is likely to have avoided future events also, meaning treatment was likely to be more cost-effective. This issue may be partially addressed by using health state costs that include future event costs where possible. Another factor the model did not consider was the variability in risk over time, which was assumed to increase linearly but might increase at a faster rate at certain time points, particularly in older people. This would increase the absolute benefit from treatment. Also, particularly in younger individuals, there are some things that might be preventable and are irreversible, such as vascular damage. There may also be other cardiovascular events that are impacted by taking antihypertensive treatment and other benefits to taking antihypertensive treatment that would also mean the model has a potentially underestimated treatment benefit. The model also used average long-term mortality ratios for mortality following cardiovascular events. This could mean the mortality immediately following an event was underestimated; thus, events in the no treatment arm would have lower QALYs if the death rate after an event was higher, making treatment even more cost-effective.

The committee generally believed that the treatment-effects used in the base-case analysis were conservative because they were based on data from studies mostly on single drug interventions.[8] Alternative sources of treatment effect that were more favourable were used in the sensitivity analyses, and as would be expected, this made treatment more cost-effective in all groups. No evidence was included in the clinical review regarding whether relative treatment effect varied by CV risk. The committee agreed that the same relative treatment effect should be applied to all risk subgroups in the model. Note that although relative risk was assumed to be constant across all risk subgroups, absolute treatment benefit still varied as baseline risk varies – this means that the balance of benefits and risks varied in the model by CV risk as might be expected in real life. Although treatment effect evidence was specific to stage 1 hypertension, it is also acknowledged that it was largely from people with intermediate or higher risk, as these are the people in the RCTs. The reason for this is that it is difficult to conduct a CV outcome study in low-risk populations due to the low event rate, which necessitates very large participant numbers and prolonged follow-up. In support of the model, observational data included in the clinical review for this question (Sheppard 2018[48]) from a matched cohort study suggested that clear evidence of benefit could not be identified in a population with average risk (where calculable) in the range 5–8% (women; men), but that an increase in adverse events (harms) was observed with additional treatment. However, this study only looked at lower risk people and did not assess whether relative treatment effects varied by risk. The study design is also less reliable for establishing treatment effects than the RCT studies. There is therefore some uncertainty as to whether the treatment effects used in the model were generalisable to the lower risk groups. If people do not derive benefit from treatment, then it will not be cost effective to treat them. Overall, the committee considered it most appropriate to use the RCT data and the assumption of constant risk, but acknowledged this uncertainty in the lower risk people.

The epidemiology data used was based on existing cost-effectiveness models, and these might be considered out-of-date (such as distributions of events, annual CV risk increase, or standardised mortality ratios). It is possible that definitions of conditions have changed over time, or treatment may have improved over time leading to reduced mortality. However, the epidemiology data was from very large registries, and the committee felt that the frequency of events relative to each other is unlikely to have changed too much over time.

Another assumption the model made was that the development and diagnosis of hypertension occured simultaneously, but it is most likely that an individual would have had undiagnosed hypertension for some time. In which case, a person may be closer to developing other reasons for becoming eligible for treatment. Although the results showed that in general, even treating for short differential treatment durations was cost-effective for most people.

The QRISK2 equation is also known to underestimate risk in younger people and overestimate risk in older people. Therefore, the conclusions of the model have to be taken with caution for those groups. The decision to treat is always based on a number of factors in practice and is a very individualised discussion. Treatment may be more cost-effective than the model showed in younger people and less cost-effective than the model showed in older people. This would still favour an overall conclusion that it was generally cost-effective to treat all, because if younger people had higher risk, then the certainty about treatment being cost-effective would be higher. Additionally, in older people, the threshold the model predicted was still very much below what their risk would be in reality, even if that was an overestimate.

It is acknowledged that adherence to treatment has not been incorporated into the model. A systematic review and meta-analysis on non-adherence to antihypertensive medications[1] found that up to around 45% of hypertensives were not adherent to their medication. The impact of not including this in the model is the potential overestimation of treatment effect on the model cohort and perhaps overestimation of cost (if people are not filling their prescriptions). Although in a trial setting, there is also unlikely to have been 100% adherence, so this may have been partly captured through the treatment effect. However, as the treatment effect in the base case was considered to be conservative, as well as other methods in the model, the impact of treatment on the conclusions of the model was felt to be, on balance, underestimating the benefit of treatment.

1.4.3 Generalisability to other populations or settings

An important point about generalisability is in relation to populations included in studies. The treatment effect used in the model is dependent on the population included in the trials. It is common that trials would have inclusion and exclusion criteria so that they capture participants from a specific population thereby excluding people who are more or less unwell, or at higher or lower risk. This could mean that the inputs in the model may be more or less generalisable to certain subgroups, and more research such as in specific groups or across different risk subgroups would be helpful for future work.

More specifically, the committee opinion, based on the population characteristics of the treatment effect trial used, was that this is likely to be more of a medium/high risk population, and therefore the results had to be interpreted with caution for lower risk people. Therefore for the model to be generalisable to lower risk individuals specifically in order to be more certain of the results in that group, then trial data would be needed specifically in lower risk populations.

1.4.4 Comparisons with published studies

No models were identified in the systematic review for the guideline that addressed this question.

It is generally accepted that hypertensive treatment is very cost-effective. To compare the results of this model to other models that have evaluated antihypertensive treatment, the 2011 hypertension guideline drugs model was looked at.[30] This model compared different first line antihypertensives and had a base-case population of a 65-year-old male with a 2% per annum CV risk. A 2% annual risk roughly equates to a 20% 10-year risk. Comparing the results of that model to the 20% risk base-case age group of the treatment initiation threshold model, showed that both models had quite low ICERs, and were therefore in agreement about the cost-effectiveness of antihypertensive treatment.

1.4.5 Conclusions

This analysis found that treating people with stage 1 hypertension (without target organ damage, established CVD, renal disease or diabetes) regardless of CV risk was cost-effective across most age and sex subgroups. The exceptions being younger women, where a risk threshold became apparent because some younger women at very low levels of risk could be below the cost-effective risk level predicted by the model (for example, below 1.86% for women aged 40).

Conclusions were somewhat sensitive to modelling assumptions regarding differential treatment duration that found that if this was short, treating younger people at low-risk may not be cost effective.

Conclusions were also sensitive to inputs like treatment effect, as using the upper confidence of the relative risks meant treatment was dominated and conversely using more favourable relative risks meant treatment became more cost-effective.

1.4.6 Implications for future research

This is thought to be the first model evaluating the risk initiation threshold at which antihypertensive treatment is cost-effective.

Further up-to-date information that would help the model include treatment effect in specific CV risk populations ideally in a UK population and using QRISK, epidemiological data on the breakdown of the distribution of CV events by age and sex, as well as cost data for CV events that include repeat events and social care.

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