National Institute for Health and Care Excellence

Draft for Consultation

Acute Coronary Syndromes

Cost-effectiveness analysis: Which dual antiplatelet therapy is most cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults undergoing PCI?

NICE guideline <number>

Economic analysis report

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Draft for Consultation

This guideline was developed by the National Guideline Centre

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Contents

1 Introduction

Dual-antiplatelet therapy (DAPT) (aspirin plus: clopidogrel, prasugrel or ticagrelor) is established practice as part of initial management of acute coronary syndrome (ACS) in order to reduce the risk of further cardiovascular events (and is generally continued post-ACS). NICE guideline CG94 updated NICE TA80 on clopidogrel in combination with aspirin for UA/NSTEMI.[37] NICE TA317 recommended prasugrel in combination with aspirin as an option for people with ACS having a percutaneous coronary intervention (PCI).[34] NICE TA236 recommended ticagrelor in combination with aspirin as an option for people with STEMI intended to be treated with primary PCI and people with UA/NSTEMI.[38] This means that all three agents are options in current NHS practice. The TAs were unable to make recommendations regarding prasugrel versus ticagrelor at the time of their development although both did consider this comparison. Audit data from 2017/18 showed that 97.5% of people who have had a myocardial infarction (MI) were discharged on clopidogrel, prasugrel or ticagrelor.[32]

However, there is uncertainty in clinical practice about which option should be used and variations in practice across England.[25] As part of the guideline update the committee therefore considered the question 'Which dual antiplatelet is most clinically and cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults'. The full review of the clinical effectiveness evidence and published cost effectiveness evidence including the committee discussion can be found in 'Evidence report A'.

All agents reduce cardiovascular events but increase bleeding and so there is a trade-off between these effects. Also, mortality could be impacted by both effects. This could result in differences in QALYs and costs downstream. RCTs have suggested benefits of prasugrel and ticagrelor over clopidogrel.

This is an important question for economic modelling as there is variation in current practice. The British Cardiovascular Intervention Society (BCIS)[24, 25] audit reported that in 2017 1.0% of people with UA/NSTEMI received prasugrel, 40.2% received ticagrelor and most of the remaining received clopidogrel. For those having PCI with STEMI, 7.2% received prasugrel, 47.5% received ticagrelor and the remaining will have received clopidogrel. Furthermore, there are considerable differences in the costs of these drugs, with ticagrelor being the most expensive option costing approximately £714 per year. Prasugrel costs approximately £152 per year and clopidogrel, costs approximately £19 per year.

There were five health economic studies identified and included in the review for this question, which all found that ticagrelor was cost-effective in comparison to clopidogrel and that prasugrel was cost-effective in comparison to clopidogrel. Some studies compared all three agents together and found ticagrelor to be the most cost effective. However, the committee considered there to still be uncertainty about the cost-effectiveness of these interventions as the treatment effects used in models did not include new clinical data identified in the clinical systematic review undertaken in the guideline, in particular head-to-head studies that compared prasugrel and ticagrelor.

As a result of this uncertainty, which DAPT combination to use in people with ACS undergoing PCI was identified as the highest priority for new economic analysis by the committee. This was because a recommendation for a particular agent would result in a significant change in clinical practice that could have a substantial resource impact for the NHS as drug costs vary substantially between agents and current practice is variable. It was agreed that new cost-effectiveness analysis could reduce the uncertainty by comparing all three agents together and incorporating the most up-to-date clinical effectiveness evidence.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken with a lifetime horizon. 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.[33] An incremental analysis was undertaken.

2.1.1 Comparators

The comparators selected for the model were:

1. Clopidogrel 75mg once daily + aspirin 75-150mg once daily (300-600mg clopidogrel loading dose) for 12 months
2. Ticagrelor 90mg twice daily + aspirin 75-150mg once daily (180mg ticagrelor loading dose) for 12 moths
3. Prasugrel 5-10mg once daily + aspirin 75-150mg once daily (60mg prasugrel loading dose) for 12 months

The analysis did not include aspirin alone as this comparison was not included in the review protocol for this question in the guideline update (see Evidence report A for review protocol) because use of DAPT is well established in ACS.

In some cases people discontinue taking their DAPT before 12 months, however, for the purpose of this analysis it was assumed that everyone alive will continue to take DAPT until the end of 12 months. It was noted by the committee that some people experiencing a major bleed may have their DAPT treatment stopped but in many cases they might restart taking DAPT. Some people that have a cerebral haemorrhage may stop taking their DAPT indefinitely, however as this would affect a small number of people it was agreed not to model this for simplification.

People presenting with an acute coronary syndrome and that are going to have a PCI, usually receive dual-antiplatelet therapy before the procedure. For those receiving ticagrelor and clopidogrel, they can start the drug immediately. However, a complication is that prasugrel is only licensed for use during PCI. The vast majority of the STEMI population will receive PCI as their primary management strategy and will receive this early on. However, for UA/NSTEMI it will not be known whether or not a PCI is suitable until angiography has been performed and this may not happen for a few days. In the model, for those with UA/NSTEMI receiving prasugrel it was assumed for costing purposes that they receive no DAPT initially, and then receive prasugrel at the time of PCI. The annual MINAP 2015/16[31] report states that the median time to angiography for NSTEMI is 65 hours, therefore it was assumed for costing purposes that people received aspirin for 3 days and then began taking prasugrel at the time of PCI.

It is acknowledged that ticagrelor can be taken beyond 12 months, however, it is indicated for use irrespective of which initial DAPT was taken, therefore it is assumed that the use of ticagrelor beyond 12 months would be the same between arms and was not incorporated in to the model.

It is also acknowledged that an existing NICE technology appraisal (TA335) recommends low dose rivaroxaban as an option in combination with aspirin plus clopidogrel after acute management of acute coronary syndrome.[35] It is beyond the scope of the guideline update to make a recommendation about the use of rivaroxaban after ACS however, as rivaroxaban is only indicated for use with clopidogrel, a recommendation for prasugrel or ticagrelor would preclude rivaroxaban's use and so it is potentially relevant to take this into account in the

analysis. The committee indicated that current usage is low therefore it was considered via a modification to the clopidogrel arm in a sensitivity analysis which is discussed in section 2.4.

2.1.2 Population

Two separate populations were analysed:

- People with STEMI undergoing PCI
- People with UA/NSTEMI undergoing PCI

Although treatment effects were being analysed together for the overall ACS population in the clinical review and meta-analyses, the committee agreed the populations should be modelled separately in the cost effectiveness analysis because they are likely to have different baseline risks. Even if relative treatment effects are considered the same between the populations, if baseline risks vary then absolute differences in numbers of clinical events will also vary and this may affect cost effectiveness.

The vast majority of STEMI patients will receive PCI. People with UA/NSTEMI are risk assessed and those at higher risk or with symptoms undergo angiography with a proportion of these going on to receive PCI where indicated. The economic analysis did not consider people with UA/NSTEMI that are medically managed. This is because prasugrel is not indicated in this population and one published UK economic analysis indicated that ticagrelor is cost-effective compared to clopidogrel in this population and additional economic analyses were not considered necessary by the committee.

For UA/NSTEMI it will not be known whether a PCI is suitable until angiography has been performed and this may not take place for a few days. The committee therefore discussed whether it was appropriate to model the UA/NSTEMI population who receive angiography rather than just the PCI population. It was agreed that this was not necessary because once angiography had been performed and the decision to not undertake PCI had been made people could then receive clopidogrel or ticagrelor. The use of a prasugrel strategy for people undergoing PCI does therefore not limit the treatment options for people not undergoing PCI. The committee also discussed whether use of a prasugrel strategy for people with UA/NSTEMI undergoing PCI would delay DAPT in people not undergoing PCI whilst waiting for angiography and if this would impact outcomes (and so should be captured in the modelling) however it was agreed that they did not think this was a significant issue and did not require incorporation into the model.

2.2 Approach to modelling

A two-part model was constructed which included a decision tree to model clinical events in the first year followed by a Markov model for long term extrapolation in order to calculate lifetime costs and QALYs for each comparator.

The initial 1 year decision tree reflects the DAPT treatment period where people receive aspirin plus either clopidogrel, prasugrel or ticagrelor. Estimates of real world UK baseline risks with aspirin plus clopidogrel were used to populate the model and differences in clinical events with prasugrel and ticagrelor were estimated by applying relative treatment effects (odds ratios) from the clinical effectiveness review and evidence syntheses. Costs and clinical events therefore vary by comparator. Details of the decision tree model structure are described in section 2.2.1.

Differential treatment effects were assumed to apply in the first year only. However, in order to fully capture the impact of the differences in clinical events in the first year it is necessary to model the rest of the lifetime of the population, which is standard practice in economic evaluation. For example, if mortality differs between comparators in the first year this will mean that a different number of people will be alive with each treatment at the end of 1 year.

Due to this, even assuming no further difference in risk of clinical events between comparators, costs and QALYs will vary for the population beyond one year. A Markov model was used for this extrapolation period and estimated risks for the population and this did not vary by initial DAPT treatment. Details of the Markov model structure are described in section 2.2.2 below.

The model was run for each of the DAPT comparators, with people starting in the decision tree for one year and then entering the Markov model which was run for repeated cycles. The time spent alive in each of the health states was calculated. By attributing costs and quality of life weights (utilities) to the people in each health state total costs and QALYs were calculated for the populations. The Markov model was run for a lifetime (for 40 years, by which time the majority of the cohort had died) in order to calculate lifetime costs and QALYs. Comparing the results for each of the comparators allowed us to identify the most cost effective intervention. See section 2.2.3 for details of how uncertainty was taken into account.

Full details of all model inputs are described in section 2.3.

Summary of key model assumptions:

- All people receive DAPT for 12 months following an ACS with PCI whilst alive and do not discontinue treatment
- Relative treatment effects based on evidence synthesised from any ACS population represent the relative treatment effects for people with STEMI and PCI and UA/NSTEMI and PCI (this is discussed in more detail in section 2.3.3)
- The probabilities of death, reinfarction and stroke after 1 year do not vary by DAPT treatment received in year 1
- People who did not experience an event in the decision tree (year 1) can only experience one event in the Markov model (either reinfarction or stroke); people who experience an event in the decision tree could not experience an event in the Markov model (this is discussed in more detail in section 2.2.2)

2.2.1 Model structure: first year treatment period decision tree

The initial 1 year decision tree reflects the DAPT treatment period where people could receive aspirin plus either clopidogrel, prasugrel or ticagrelor. Following the review of clinical evidence and committee discussion, it was agreed that the following outcomes needed to be captured in the 1 year model as they potentially vary between DAPT options:

- All-cause mortality
- Reinfarction
- Stroke
- Major bleed
- Minor bleed

There was some uncertainty in the committee about the inclusion of stroke as the treatment effects estimated in the clinical review had wide confidence intervals and were considered somewhat uncertain. However, previous models in this area have generally included stroke (including the NICE TAs for prasugrel and ticagrelor) and so it was agreed that it should be included.

The committee also discussed the importance of other treatment effects, and agreed that a considerable amount of people taking ticagrelor may experience breathing difficulties (dyspnoea) as a side effect. This was demonstrated in the clinical review. It was discussed and the committee agreed that this was not a critical outcome as the numbers seen in real world practice are quite low and did not need to be considered in the base case analysis but was modelled as part of a sensitivity analysis, which is discussed further in section 2.4.

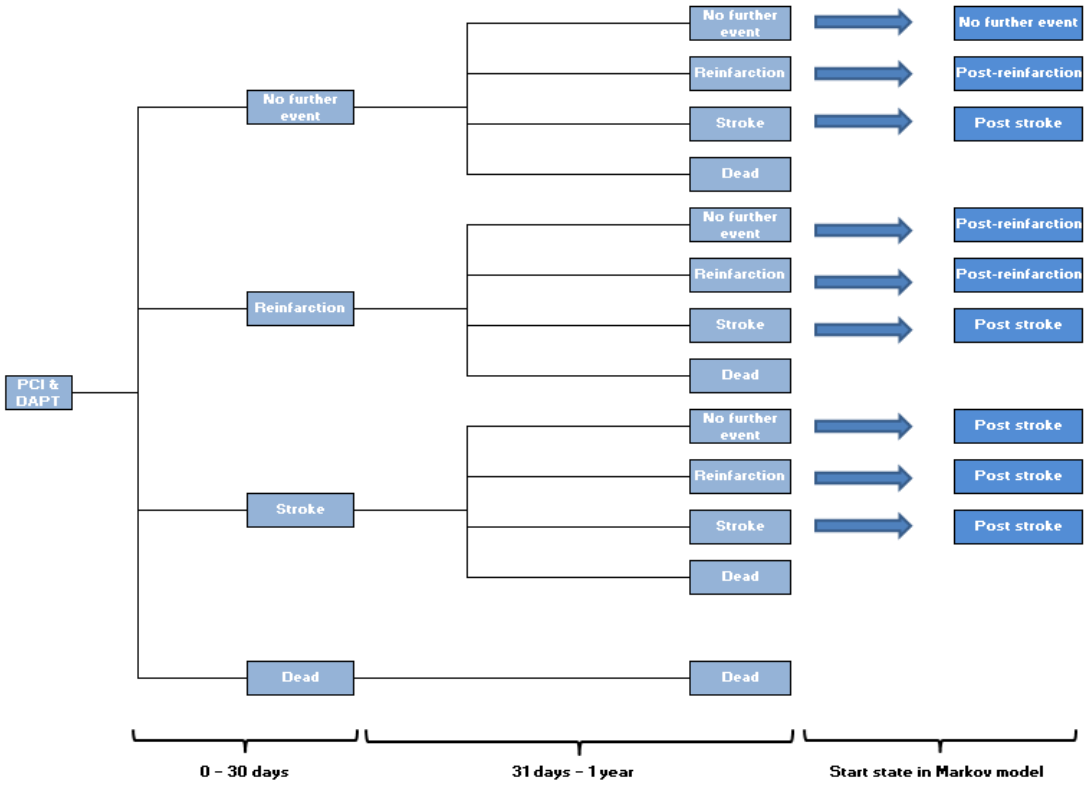
The first year decision tree was broken down into two time periods: 0 to 30 days and 31 days to 1 year as this was considered to make best use of the available clinical data, in particular incorporating new studies that directly compared prasugrel and ticagrelor. The clinical evidence review found outcome data at different time points including at 30 days and 1 year. Many of the new studies comparing prasugrel and ticagrelor directly only had 30 day outcomes, although late in development ISAR-REACT 5 published which had 1 year outcomes. A network meta-analysis (NMA) was undertaken to combine all 30 day evidence together into a simultaneous set of treatment effects and this was utilised in the model for the 0 to 30 day period. There was inconsistency between the direct and indirect estimates at 1 year and so NMA was considered unreliable and not undertaken. Instead three different treatment effect scenarios were used for the 31 day to 1 year period of the model that incorporated different clinical data and explored the impact of the inconsistency on conclusions about cost effectiveness. More details about the relative treatment effect data used in the model and the inconsistency in the 1 year outcome data are given in section 2.3.3.

The decision tree included four potential health outcomes at each time point in the decision tree: alive with no further event, alive with reinfarction, alive with stroke and dead. Major and minor bleeding were incorporated as adverse events as the effects were considered to be short-term (except for haemorrhagic stroke which is captured in the stroke outcome). People alive at the end of the 1 year period entered the post-year one Markov model to extrapolate 1 year outcomes to a lifetime perspective. Figure 1 illustrates the structure of the decision tree and which health states people enter the Markov model. The rationale for where people enter the Markov model is discussed in the next section.

It was acknowledged that the major bleeding and stroke outcomes overlap as the stroke outcome included both ischemic and haemorrhagic strokes and a haemorrhagic stroke will also be counted as a major bleed. However, it was felt that capturing strokes explicitly was important as while they were uncommon they have a substantial and sustained impact on health and resource use. Major bleeding however is not a separate health state but is a short-term adverse effect and rates of haemorrhagic stroke are low so the committee agreed that the impact on results should not be large and capturing both strokes and major bleeds was the best approach for modelling purposes.

The model structure was the same for STEMI and UA/NSTEMI analyses.

Figure 1: Model structure: one year treatment period decision tree



Note: Probabilities of events are dependent on DAPT being received. People who are alive are also at risk of a short-term major or minor bleeding adverse event.

2.2.2 Model structure: post-one year extrapolation Markov model

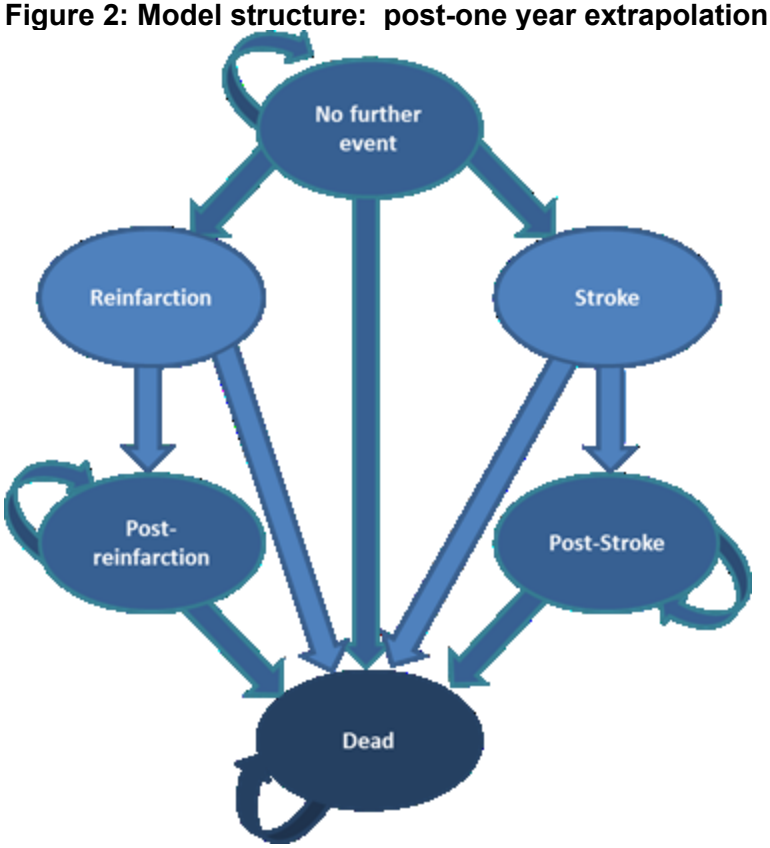
In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability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

The Markov model consisted of six health states. These included: no further event, reinfarction, post-reinfarction, stroke, post-stroke and dead. Those that were alive and had experienced no further events at the end of the decision tree entered the 'no further event' health state in the Markov model. Those that had experienced reinfarction (either once or twice) at the end of the decision tree entered the 'post-reinfarction' health state. Those that had experienced a stroke at the end of the decision tree entered the 'post-stroke' health state. For those that experienced both a stroke and reinfarction, it was discussed and agreed with the committee that they should enter the post-stroke health state, as this is the worse health state with substantially higher costs and there may be overlap in treatment received for having reinfarction and having a stroke. Also, those that experienced two strokes or two reinfarctions entered the same health state in the Markov model, which is a simplification for modelling purposes.

Figure 2 illustrates the Markov model structure and the possible transitions between health states. The Markov model used a 1 year cycle length. People in the no further event health state had the possibility of transitioning to reinfarction, stroke or dead. Reinfarction and stroke were tunnel health states, meaning that people only remain in that health state for one cycle, at which point they must transition to dead or the post-reinfarction/post-stroke health

states. The reason for including these tunnel health states is to account for the fact that in the first year after a major event, people will have higher costs, lower quality of life and a higher risk of mortality. Once someone is in the post-reinfarction or post-stroke health state, they cannot experience another event and so either remain in that state or move to the dead state (this includes those that entered the Markov model in the post-event health states). This is a simplification of reality but was considered reasonable for modelling purposes due to the lack of data available to model downstream further events. Also, this is a method employed by other cardiovascular models such as the ticagrelor NICE technology appraisal (TA236), a health technology assessment for clopidogrel and aspirin in NSTEMI[26] and a previous model looking at glycoprotein antagonists in NSTEMI in the UK.[40] This was taken into account when selecting model inputs where possible; for example, cost estimates for a health state that incorporated repeat events were used if available. Dead was an absorbing health state.

Figure 2: Model structure: post-one year extrapolation Markov model



Notes: 1 year cycles; model was run for 40 years at which point most people will be in the dead state; the state people enter model depends on events experienced in year 1 decision tree.

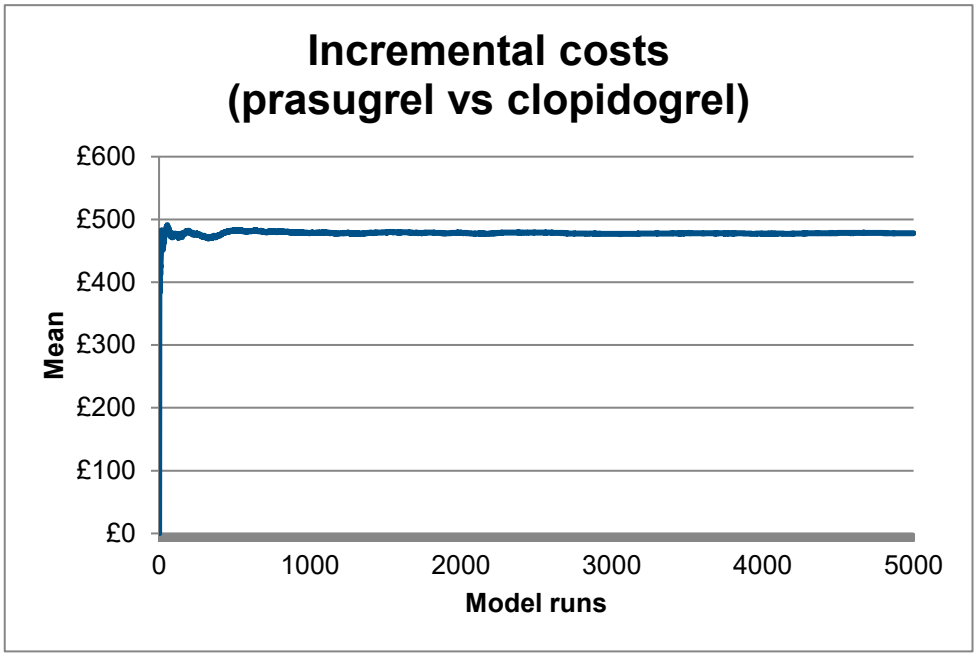
2.2.13 Uncertainty

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; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case and each sensitivity analysis – and results were summarised in terms of mean costs and QALYs. The percentage of time each comparison was most cost-effective at a threshold of £20,000 per QALY gained was recorded.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis it was checked for convergence in the incremental costs, QALYs and net monetary benefit at a threshold of £20,000 per QALY gained for each comparator. This

was done by plotting the number of runs against the mean outcome at that point (see example in Figure 3) for the base-case analysis. Convergence was assessed visually and all had stabilised before 5000 runs.

Figure 3: Checking for convergence: incremental costs (prasugrel vs clopidogrel)



The way in which distributions are 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 a probability 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. 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
Baseline risks	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)
Odds ratios at 1 year Hazard ratios SMRs	Lognormal	The natural log of the mean was calculated as follows: Mean = ln(mean cost) − $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$
Odds ratios (30 days)	Bespoke	The network meta-analysis used simulation methods, which yielded 60,000 individual estimates of each odds ratio. These estimates represent the posterior

Parameter	Type of distribution	Properties of distribution
		distribution of the odds ratio. A sample of 5,000 preserving correlations was taken from the 60,000 estimates.
Utilities	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: $Alpha = mean^2 \times [(1-mean)/SE^2] - mean$ $Beta = Alpha \times [(1-mean)/mean]$
Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: $Alpha = (mean/SE)^2$ $Beta = SE^2/Mean$

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)
- Health state costs (based on analyses that use unit costs from UK national sources)
- Drug costs (based on drug tariff which is fixed)
- Mortality probabilities for general population (based on UK national data)

In addition, various one way and scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.4.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline and 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 that follow.

Table 2: Summary of base-case model inputs

Input	Data	Source
Comparators	• Clopidogrel & aspirin • Ticagrelor & aspirin • Prasugrel & aspirin	
Populations	• Adults with STEMI undergoing PCI • Adults with UA/NSTEMI undergoing PCI	
Perspective	UK NHS and PSS	NICE reference case
Time horizon	Lifetime	NICE reference case

Input	Data	Source
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case
Baseline risks with clopidogrel 0 to 30 days		
STEMI		
All-cause mortality	6.15%	Mortality tracked BCIS PCI audit data, Hulme 2019[16]
Reinfarction	2.91%	Krishnamurthy 2019[20]
Stroke	0.30%	UK audit of PCI data, Myint 2016[30]
Major bleed	0.94%	Calculated based on relationship between bleeds and 30 day an 1 year events from PLATO RCT (see section 2.3.2)
Minor bleed	0.71%	Calculated based on relationship between bleeds and 30 day an 1 year events from PLATO RCT (see section 2.3.2)
UA/NSTEMI		
All-cause mortality	1.79%	Mortality tracked BCIS PCI audit data, Hulme 2019[16]
Reinfarction	1.02%	Calculated based on 1 year rate from NICE CG94[37] using PLATO and Swedeheart rates (see section 2.3.2)
Stroke	0.11%	UK audit of PCI data, Myint 2016[30]
Major bleed	0.65%	PLATO RCT, Lindholm 2014[23]
Minor bleed	0.41%	Calculated based on relationship between bleeds and 30 day and 1 year events from PLATO RCT (see section 2.3.2)
Baseline risks with clopidogrel 31 days to 1 year		
STEMI		
All-cause mortality	3.80%	Mortality tracked BCIS PCI audit data, Hulme 2019[16]
Reinfarction	3.88%	Krishnamurthy 2019[20] and recalculated based on 30 day events (see section 2.3.2)
Stroke	1.01%	Calculated based on 30 day events from Myint 2016[30] using Swedeheart audit data (see section 2.3.2)
Major bleed	2.69%	Steg 2010[48]
Minor bleed	2.03%	Calculated based on relationship between bleeds and 30 day an 1 year events (see section 2.3.2)
UA/NSTEMI		
All-cause mortality	3.71%	Mortality tracked BCIS PCI audit data, Hulme 2019[16]
Reinfarction	3.26%	NICE CG94[37] and recalculated based on 30 day events (see section 2.3.2)
Stroke	0.53%	Calculated based on 30 day events from Myint 2016[30] using Swedeheart audit data (see section 2.3.2)
Major bleed	1.77%	Lindholm 2014[23]
Minor bleed	1.12%	Calculated based on relationship between bleeds and 30 day an 1 year events (see section 2.3.2)

Input	Data	Source
Relative treatment effects versus clopidogrel applied 0 to 30 days (odds ratios; 95% CI)		
Ticagrelor		
All cause- mortality	0.84 (0.69 to 1.01)	Systematic review of RCTs undertaken as part of guideline development (network meta-analysis) – see Evidence report A and NMA report
Reinfarction	0.68 (0.55 to 0.84)	
Stroke	1.28 (0.86 to 1.83)	
Major bleed	1.00 (0.89 to 1.11)	
Minor bleed	1.28 (0.88 to 1.81)	
Prasugrel		
All-cause mortality	0.82 (0.64 to 1.03)	Systematic review of RCTs undertaken as part of guideline development (network meta-analysis) – see Evidence report A and NMA report
Reinfarction	0.80 (0.65 to 0.98)	
Stroke	0.84 (0.46 to 1.39)	
Major bleed	0.99 (0.61 to 1.52)	
Minor bleed	0.74 (0.51 to 1.04)	
Relative treatment effects applied 31 days to 1 year (odds ratios; 95% CI)		
Ticagrelor versus clopidogrel (used in scenarios 1 and 3)		
All-cause mortality	0.77 (0.68 to 0.88)	Systematic review of RCTs undertaken as part of guideline development (pairwise meta-analysis; 1 year outcomes) – see Evidence report A
Reinfarction	0.81 (0.72 to 0.92)	
Stroke	1.13 (0.89 to 1.44)	
Major bleed	1.04 (0.95 to 1.14)	
Minor bleed	1.37 (1.19 to 1.57)	
Prasugrel versus clopidogrel (used in scenarios 1 and 2)		
All-cause mortality	1.00 (0.83 to 1.21)	Systematic review of RCTs undertaken as part of guideline development (pairwise meta-analysis; 1 year outcomes) – see Evidence report A
Reinfarction	0.75 (0.66 to 0.84)	
Stroke	0.93 (0.67 to 1.30)	
Major bleeding	1.43 (1.14 to 1.79)	
Minor bleeding	2.07 (0.88 to 4.87)	
Ticagrelor versus prasugrel (used in scenarios 2 and 3)		
All-cause mortality	1.24 (0.90 to 1.70)	Systematic review of RCTs undertaken as part of guideline development (ISAR-REACT 5 analysis; 1 year outcomes) – see Evidence report A
Reinfarction	1.63 (1.17 to 2.26)	
Stroke	1.16 (0.62 to 2.14)	
Major bleed	1.06 (0.78 to 1.44)	
Minor bleed	*Note: No data reported in ISAR-REACT 5 for minor bleed*	
Transition probabilities in post year 1 Markov model		
Transition probabilities excluding death		
STEMI		
Reinfarction	4.30%	Calculated from baseline risk data between 31 days and 1 year for STEMI and readjusted to reflect 1 year probability
Stroke	1.01%	
UA/NSTEMI		
Reinfarction	3.62%	Calculated from baseline risk data between 31 days and 1 year for UA/NSTEMI and readjusted to reflect 1 year probability
Stroke	0.59%	
Transition probabilities to dead state		

Input	Data	Source
General population mortality	Age and sex dependent Age entering Markov model: • STEMI: ○ Male: 62 years ○ Female: 69 years • UA/NSTEMI: ○ Male: 64 years ○ Female: 69 years % male entering Markov model • STEMI: 75% • UA/NSTEMI: 72%	ONS life tables for England 2015-17[39] BCIS PCI audit data, Hulme 2019[16]
No further event SMR	2.00 (1.99 to 2.01)	Smolina 2012[47]
Reinfarction SMR	4.50 (4.43 to 4.57)	Smolina 2012[47]
Post-reinfarction SMR	3.00 (2.95 to 3.05)	Smolina 2012[47]
Stroke SMR	4.73 (4.34 to 5.15)	Bronnum-Hansen 2001[5]
Post-stroke SMR	2.37 (2.17 to 2.49)	Bronnum-Hansen 2001[5]
Costs		
Treatment costs (cost per year)		
Aspirin	£9	Includes loading dose where applicable. Unit costs and dosing from British National Formulary[18]
Clopidogrel	£19	
Prasugrel	£152	
Ticagrelor	£714	
Decision tree costs (0 – 30 day event; 31 day to 1 year event)		
No further event; no further event	£1,640	See section 2.3.6.2
No further event; reinfarction	£5,564	See section 2.3.6.2
No further event; stroke	£15,203	See section 2.3.6.2
No further event; death	£1,168	See section 2.3.6.2
Reinfarction; no further event	£5,104	See section 2.3.6.2
Reinfarction; reinfarction	£8,792	See section 2.3.6.2
Reinfarction; stroke	£18,431	See section 2.3.6.2
Reinfarction; death	£4,396	See section 2.3.6.2
Stroke; no further event	£17,323	See section 2.3.6.2
Stroke; reinfarction	£21,719	See section 2.3.6.2
Stroke; stroke	£21,014	See section 2.3.6.2
Stroke; death	£14,035	See section 2.3.6.2
Death; n/a	£0	
Adverse event costs		
Major bleed	£1,955	NHS reference costs 2017/18[11], weighted average of gastrointestinal bleeds with interventions

Input	Data	Source
Minor bleed	£176	NHS reference costs 2017/18[11], weighted average of emergency admission with investigation
Markov model costs		
No further event	£943	Danese 2016[8]
Reinfarction	£5,104	Danese 2016[8]
Post-reinfarction	£1,415	Danese 2016[8]
Stroke	£18,522	Xu 2018 SSNAPP project[59]
Post-stroke	£3,748	Xu 2018 SSNAPP project[59]
Quality of life (utilities)		
Health states		
No further event	0.842	NICE TA236[38] PLATO health economic subgroup analysis
Reinfarction	0.779	
Post-reinfarction	0.821	
Non-fatal stroke	0.703	
Post-stroke	0.703	
Dead	0	By definition
Age-adjustment (general population utility by age)	Age and sex dependant	Calculated using formulae from Ara and Brazier 2010.[3] Applied multiplicatively with health state weights.
Adverse event decrements (and duration applied)		
Major bleed	0.038 (45.38 days)	Amin 2016[12]
Minor bleed	0.026 (7.60 days)	

Abbreviations: ONS = Office for National Statistics; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; SMR = standardised mortality ratio

2.3.2 Baseline risks in first year treatment period decision tree

The model was populated with baseline risks for those receiving clopidogrel and aspirin (e.g. the probability of death at 30 days etc). When running the model for those receiving ticagrelor and prasugrel a relative treatment effect obtained from the clinical review and evidence synthesis (compared to clopidogrel) was applied to this in order to estimate the difference in number of events with these alternative treatments. The relative treatment effects are discussed in section 2.3.3.

2.3.2.1 The available data and general issues

The data required for the baseline risks in the first year decision tree was the proportion of people who have died, and who are alive with reinfarction, stroke or no event at 30 days and at 1 year after STEMI and after UA/NSTEMI in people receiving clopidogrel and aspirin. The potential to undertake original analysis of real world patient level data using national audit data linked with mortality and HES data was discussed as this would allow exact calculation of the probabilities required for the model but this was not feasible within guideline development time constraints. Therefore, published analyses of real world risks utilising UK audit data were sought and presented to the committee for discussion of the best available data sources.

No data source was identified that reported data exactly as required however a number of separate UK real-world analyses provided information about mortality, stroke and reinfarction after STEMI and UA/NSTEMI and these were used to estimate the required probabilities for the decision tree. The data used in the model to inform probabilities for each outcome is

described in the subsequent sections in detail. Some general issues and the approach taken are described below first.

One issue was that the model aims to estimate the number of people alive at a particular time point with stroke or reinfarction but the available data analyses mostly looked at all events over the time period (reinfarction for STEMI and stroke for STEMI and UA/NSTEMI was based on all events and reinfarction for UA/NSTEMI was based on non-fatal events). Where this was the case this data has been used but it is acknowledged this may results in an overestimate of the number of people alive having had these events at 1 year and so also underestimate the number alive with no new event (note that the number of people alive will not be affected just whether or not they have an event). Given this a sensitivity analysis was undertaken using lower probabilities for stroke and reinfarction (as described in section 2.4) to explore whether conclusions were sensitive to this.

Another issue was whether probabilities between 31 days and 1 year should vary depending on what happened between 0 and 30 days. While the committee agreed that in reality it may be the case that prior events will influence these probabilities, the real world UK data identified were for the population as a whole. The committee discussed whether to try and adjust the probabilities to try and account for this but preferred to use the same probability throughout given the available information and agreed that this was a reasonable simplification for modelling purposes given the overall number of people alive in the population will remain correct. Therefore in the model, the same probability of having an event (death, MI or stroke) between 31 days and 1 year was applied irrespective of whether someone experienced MI, stroke or no new event between 0 to 30 days.

Data relating to people with ACS receiving clopidogrel and aspirin were sought however audit data was mostly analysed for the overall cohort, rather than just those that received this dual antiplatelet option. The committee noted that there may be issues with using the most recent audit data for the baseline risks. Firstly, they stated that a high proportion of people will not be taking clopidogrel as the use of ticagrelor and prasugrel has increased in recent years. For those that are on clopidogrel it may be that these people have a higher bleeding risk (e.g. an older population) and therefore were given clopidogrel, which would not be a good representation of the average population.

Therefore the committee felt that it may be useful to use slightly older audit data to account for this. It was highlighted that a balance would have to be taken between choosing a year where clopidogrel use was high but also ensuring that it was still relevant to current practice in terms of other processes, for example, radial access and drug-eluting stent usage. Therefore, BCIS reports were used to obtain the DAPT use for each year in order to help aid committee decisions regarding which data to use. The specific data used in the model and the rationales are described in the sections that follow by outcome.

Table 3: BCIS audit data[25]

	2010	2011	2012	2013	2014	2015	2016	2017
STEMI								
Prasugrel	9.3%	22.2%	22.6%	16.1%	14.1%	10.5%	9.9%	7.2%
Ticagrelor	n/a	n/a	7.04%	21%	30.1%	38.1%	42.2%	47.5%
Clopidogrel[(a)]	90.7%	77.8%	70.4%	62.9%	55.8%	51.4%	47.9%	45.3%
DES use	54.4%	59.5%	68.4%	75.8%	81.9%	86.3%	89.1%	91.0%
Radial access	50.0%	57.0%	65.5%	71.5%	75.8%	80.3%	82.8%	85.8%
UA/NSTEMI								
Prasugrel	0.54%	1.5%	2.6%	1.9%	1.6%	1.6%	1.1%	1.0%
Ticagrelor	n/a	n/a	3.7%	15.2%	23.0%	29.9%	34.3%	40.2%
Clopidogrel[(a)]	99.5%	98.5%	93.7%	82.9%	75.4%	68.5%	64.6%	58.8%

	2010	2011	2012	2013	2014	2015	2016	2017
DES use	66.6%	69.8%	76.8%	82.5%	86.9%	89.7%	90.9%	91.5%
Radial access	54%	62%	66.7%	71.9%	75.6%	79.8%	83%	85.8%

(a) Clopidogrel use was not always reported therefore it was assumed that everyone not receiving prasugrel or ticagrelor was receiving clopidogrel.

Calculating probabilities for 31 days to 1 year

To calculate probabilities for 31 days to 1 year, the appropriate numerator (r) and denominator (n) needed to be calculated from the data for this time period. That is the numerator needed to only include events that occurred between 31 days and 1 year and the denominator needed to only include those at risk at 31 days (i.e. those alive).

$$\text{Probability of event 31 days to 1 year} = \frac{\text{events 31 days to 1 year (r)}}{\text{people at risk at 31 days (n)}}$$

Events 31 days to 1 year (r) = events at 1 year – events at 30 days

People at risk at 31 days (n) = total population – people who died 0 to 30 days

As the data analyses identified for each outcome (other than mortality) did not generally report the actual number of people who had died by 30 days this was estimated by multiplying the total population by the 0 to 30 day mortality probability used in the model.

Details of the calculations for each outcome are described in subsequent sections.

Incorporation of baseline risk into probabilistic analysis

Each baseline risk probability was incorporated into the probabilistic analysis using an independent beta distribution. These were parameterised using the relevant number of events (r) and number of people at risk (n).

While theoretically the four alternative outcomes at each timepoint would be incorporated using a Dirichlet distribution (used for multinomial data) this was not possible here as not all the probabilities came from the same source. However, checks were built into the model to ensure the overall probabilities generated were appropriate (not exceeding one or negative) and so this is not considered problematic.

In addition it was noted that there may be covariance between probabilities in the model however data was not available to incorporate this and so independent distributions were used. This is a common approach in cost effectiveness modelling.

2.3.2.2 Mortality

A study by Hulme 2019[16] reported crude and relative survival estimates at 30 days and 1 year for males and females following PCI for England and Wales in the years 2007 to 2014. This analysis was based on mortality tracked BCIS PCI audit data and STEMI and UA/NSTEMI were reported separately. Although the study did not report survival based on clopidogrel use, it was agreed to use a year where BCIS reported higher clopidogrel use (as seen in Table 3), and as a result the year 2011-12 was chosen as clopidogrel use was 77.8% for STEMI and 98.5% for UA/NSTEMI. The data on crude survival was used to obtain the 30

day and 1 year probability of death as demonstrated in Table 4. These were then combined to obtain the overall probabilities for males and females, based on a weighted average.

Table 4: Hulme 2019 survival and mortality calculations

	30 days crude survival	30 day mortality[(a)]	1 year crude survival	1 year mortality[(a)]
STEMI				
Female	0.914	1 – 0.914 = 8.6%	0.865	1 – 0.865 = 13.5%
Male	0.947	1 – 0.947 = 5.3%	0.916	1 – 0.916 = 8.4%
All (male & female)		6.15%		9.71%
UA/NSTEMI				
Female	0.977	1 – 0.977 = 2.3%	0.937	1 – 0.937 = 6.3%
Male	0.984	1 – 0.984 = 1.6%	0.949	1 – 0.949 = 5.1%
All (male & female)		1.79%		5.43%

(a) The probability of mortality at 30 days and 1 year were calculated using the crude survival.

As described in more detail in Section 2.3.2.1 above, the model structure in the first year was split to model 0 to 30 days and 31 days to 1 year, calculation of the probabilities for 31 days to 1 year needed to account for people who had died at 30 days in the numerator and denominator. Table 5 shows the calculations and resulting model inputs for mortality for STEMI and UA/NSTEMI.

Table 5: Data inputs for mortality baseline risk in STEMI and UA/NSTEMI

N	R	Probability	N	R	Probability
STEMI					
30 days			1 year		
40,724	2,504	6.15%	40,724	3,955	9.7%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
40,724	2504	6.15%	40,724 – 2,504 = 38,220	3,955 – 2,504 = 1,451	1,451/38,220 = 3.80%
UA/NSTEMI					
30 days			1 year		
54,518	978	1.79%	54,518	2,962	5.43%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
54,518	978	1.79%	54,518 - 2,962 = 53,540	2,962 – 978 = 1,984	1,984/53,540 = 3.71%

2.3.2.3 Reinfarction

An analysis of reinfarction using national STEMI data was not identified. Krishnamurthy 2019 however reported an analysis of real world data in Leeds comparing the differences in outcomes of people taking clopidogrel, ticagrelor and prasugrel at 30 days and 1 year.[20] This was a study conducted at Leeds General Infirmary and assessed all adults with STEMI that underwent primary PCI between 1 January 2009 and 31 December 2011. The committee agreed this was a reasonable source of baseline risk estimates given national data wasn't available. Table 6 shows the number of people and probability of reinfarction taken from the study. As discussed in more detail above, this probability was for all reinfarctions, and

therefore would overestimate the number of people alive with a reinfarction at 1 year. This was addressed in a sensitivity analysis to see if this impacted conclusions.

As described in more detail in Section 2.3.2.1 above, calculation of the probability for 31 days to 1 year for the model needed to account for events that occurred 0 to 30 days in the numerator and people who had died by 30 days in the denominator. Table 7 shows how these were adjusted to obtain the probabilities for 0 to 30 days and 31 days to 1 year.

Table 6: Reinfarction for STEMI population from Krishnamurthy 2019

n	r at 30 days	Probability of reinfarction at 30 days	r at 1 year	Probability of reinfarction at 1 year
1,648	48	48/1,648 = 2.91%	108	108/1,648 = 6.55%

Abbreviations: n = number of people in the study; r = number of events

Table 7: Data inputs for reinfarction baseline risk in STEMI

N	R	Probability	N	R	Probability
30 days			1 year		
1648	48	2.91%	1648	108	6.55%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
1648	48	2.91%	1648 – (1648*6.15%[a]) = 1547	108 – 48 = 60	60/1547 = 3.88%

(a) This is the probability of death at 30 days, taken from Hulme 2019[16]

For the UA/NSTEMI population undergoing PCI, the best available source identified was an analysis of MINAP data that was conducted for the previous UA/NSTEMI NICE Guideline CG94.[37] This analysis reported reinfarction at 1 year and reported it separately by type of management, therefore it was available for those who underwent PCI. This analysis was conducted for people with UA/NSTEMI in England from 2005 to 2007. It was discussed that this was quite an old analysis and that treatment may have improved since then, for example, the guideline recommended the use of early angiography and PCI if indicated, meaning that more people with UA/NSTEMI have undergone PCI since then. Only 15% of the people analysed in this dataset underwent PCI. However, one of the positives of using this data was that it was specific to PCI and also the use of ticagrelor and prasugrel had not started, meaning everyone in the analysis would have received clopidogrel. As a result, the committee agreed this was the best available source of data available to estimate baseline risk. Also, the probabilities were for non-fatal events, therefore the correct number of people alive with a reinfarction at one year was available. As a result these were not adjusted in a sensitivity analysis. Table 8 shows the events and probabilities. The committee considered using more recent data from the Swedish national audit Swedeheart as this had published an analysis of UA/NSTEMI outcomes in Sweden including reinfarction[50]. However, UA/NSTEMI overall was analysed and only 47.3% had PCI so the committee agreed the MINAP analysis was preferable.

Table 8: CG94 probability of reinfarction

n	r at 1 year	Probability of reinfarction at 1 year
2,392	101	101/2392 = 4.22%

Abbreviations: n = number of people in the study; r = number of events

As the MINAP analysis did not report reinfarction at 30 days, this was estimated using the 1 year data combined with information about the proportion of 1 year events that happen between 0 and 30 days. The committee agreed the best source of information about this relationship identified was the Swedeheart audit described above.[50] However, as there was some uncertainty due to this analysis not only including people receiving PCI, the committee

also wanted to know the relationship between 30 day and 1 year events in the clopidogrel arm of the PLATO RCT[52], as this was the trial which was considered closest to UK practice, as it was the only trial to recruit in the UK. This was only available for the overall ACS population and was not specific to UA/NSTEMI. Table 9 shows the probability of reinfarction at 30 days and one year from Swedeheart and PLATO, and the resulting proportions of 1 year events that occurred by 30 days.

Table 9: Relationship between 30 day and 1 year events for reinfarction

	n	Probability of reinfarction
Swedeheart 2011-2012		
30 day	24,962	2.0%
1 year	24,962	9.9%
Proportion of events that occurred by 30 days		2.0%/9.9% = 20.2%
PLATO		
30 day	9186[(a)]	1.8%
1 year	9291	6.4%
Proportion of events that occurred by 30 days		1.8%/6.4% = 28.1%
Calculated 30 day probability of reinfarction		
Average proportion of 30 days to 1 year		(20.2+28.1)/2 = 24.2%
Calculated 30 day probability of reinfarction		24.2% * 4.22% = 1.02%

(a) Note: the authors were contacted for 30 day outcomes and the number of participants was slightly different to those reported in the published paper

The committee decided to average the percentage obtained from the Swedeheart and PLATO analysis in order to calculate the probability of reinfarction at 30 days as these estimates were similar. Again, adjustments were made in order to obtain the correct number of events between 31 days and 1 year (r) and the total number of people at risk at 31 days (n) in order to calculate the probability of reinfarction 31 days to 1 year. Table 10 shows how the baseline risk was adjusted for reinfarction in UA/NSTEMI.

Table 10: Data inputs for reinfarction baseline risk in UA/NSTEMI

N	R	Probability	N	R	Probability
30 days			1 year		
2,392	24	1.02%	2,392	101	4.22%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
2,392	24	1.02%	2,392 – (2,392*1.79%[a]) = 2,349	101 – 24 = 77	77/2,349 = 3.26%

(a) This is the probability of death at 30 days, taken from Hulme 2019[16]

2.3.2.4 Stroke

Data on 30 day probability of stroke was taken from Myint 2016[30], which looked at outcomes of stroke following PCI based on BCIS audit data. As described in more detail in Section 2.3.2.1 above, fatal and non-fatal events were included in this data, and therefore will somewhat overestimate the number of people alive with a stroke at 1 year. This was addressed in a sensitivity analysis to see if this impacted conclusions.

Table 11: Myint 2016[30] stroke outcomes at 30 days

n	r (ischaemic stroke)	r (haemorrhagic stroke)	r (all stroke)	Probability of stroke at 30 days
STEMI				
102,493	256	48	304	304/102,493 = 0.30%
UA/NSTEMI				
205,962	181	41	222	222/205,962 = 0.11%

As there was no real world data for 1 year outcomes of stroke, data from Swedeheart and PLATO was used to calculate the relationship between 30 day and 1 year events, as seen in Table 12.

Table 12: Relationship between 30 day and 1 year events for stroke

	n	Probability of stroke
Swedeheart STEMI 2011-2012		
30 day	117,546	0.5%
1 year	117,546	2.1%
Percentage increase 1 year relative to 30 days		2.1%/0.5% = 420%
Swedeheart UA/NSTEMI 2011-2012		
30 day	24,962	0.5%
1 year	24,962	2.9%
Percentage increase 1 year relative to 30 days		2.9%/0.5% = 580%
PLATO (overall ACS)		
30 day	9186[(a)]	0.5%
1 year	9291	1.1%
Percentage increase 1 year relative to 30 days		1.1%/0.5% = 224%
Calculated 1 year probability for stroke		
Calculated 1 year probability of stroke for STEMI		420% * 0.30% = 1.25%
Calculated 1 year probability of stroke for UA/NSTEMI		580% * 0.11% = 0.63%

(a) Note: the authors were contacted for 30 day outcomes and the number of participants was slightly different to those reported in the published paper

The estimates obtained from Swedeheart and PLATO were quite different, therefore the committee agreed to use the Swedeheart estimates for both STEMI and UA/NSTEMI in the base case analysis as it is based on large registry data. However due to the differences between the two sources, it was agreed to conduct a sensitivity analysis using the PLATO estimate to assess if this impacted conclusions. The results of this calculation are demonstrated in Table 12. Adjustments were made in order to have the correct number of events between 31 days and 1 year (r) and the total number of people at risk at 31 days (n), in order to calculate the probability of stroke between 31 days and 1 year. Table 13 shows the calculations to obtain these probabilities.

Table 13: Data inputs for stroke baseline risk in STEMI and UA/NSTEMI

N	R	Probability	N	R	Probability
STEMI					
30 days			1 year		
102,493	304	0.30%	102,493	1,277	1.25%

N	R	Probability	N	R	Probability
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
102,493	304	0.30%	102,493 – (102493*6.15% [a]) = 96,190	1,277 – 304 = 973	973/102,493 = 1.01%
UA/NSTEMI					
30 days			1 year		
205,962	222	0.11%	205,962	1,288	0.63%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
205,962	222	0.11%	205,962 – (205,962*1.79% [a]) = 202,266	1,288 – 222 = 1,066	1,066/202,266 = 0.53%

(a) This is the probability of death at 30 days, taken from Hulme 2019[16]

2.3.225 Major and minor bleeding

Suitable real world data about major and minor bleeding for the specific populations in the model were not identified. As a result, the committee agreed that estimates from the PLATO RCT should be used. This was because the committee indicated that this trial was closest to UK practice.

As haemorrhagic stroke would be classified as a major bleed but also be captured in the stroke health state, the major bleeding rate should ideally exclude haemorrhagic stroke to account for double counting. However, the major bleeding rate was not reported without haemorrhagic stroke. As major bleeding was incorporated as a short-term adverse event it was deemed appropriate to assume that there was no overlap for the purposes of the model.

Overall major and minor bleeding rates looked very high in the PLATO RCT, and this was thought to be because their definition of bleeding included CABG related bleeding. They also reported other bleeding outcomes according to different definitions and it was decided by the committee to use the definition which excluded CABG bleeding. However, these were not well reported. Table 14 shows the data that was available on non-CABG major and minor bleeding.

Table 14: Data available from published sources for non-CABG related bleeding from PLATO

	Major bleed	Minor bleed
STEMI		
30 day	NR	NR
1 year	3.46%	2.61%[(a)]
UA/NSTEMI		
30 day	0.65%	NR
1 year	2.38%	NR

Abbreviations: NR = not reported

(a) This was calculated from published data, using the total number of non-CABG major and minor bleeds and subtracting the number of major bleeds.

As seen above, there was no data available on minor bleeds for UA/NSTEMI and there was no data on major bleeds at 30 days and minor bleeds for STEMI. As a result, calculations were undertaken to estimate the probabilities.

To estimate the number of major bleeds at 30 days for STEMI, the relationship between 30 day and 1 year events for UA/NSTEMI was applied. For UA/NSTEMI 27% of 1 year events occurred in 30 days. Using this combined with the 1 year STEMI major bleeding rate resulted in an estimated probability of major bleed at 30 days of 0.94% for STEMI. The relationship of 30 day and 1 year events from UA/NSTEMI was used again to obtain the probability of minor bleeds at 30 days, which was 0.71%.

In order to calculate minor bleeds for UA/NSTEMI, the relationship between major and minor bleeds was estimated from a different outcome for bleeding, based on the TIMI criteria. This was deemed appropriate as the probabilities were similar for bleeding events where they reported the same outcome (e.g. major bleeds). Table 15 shows how this was calculated.

Table 15: Calculations for UA/NSTEMI minor bleed

Outcome	Probability
Major bleed at 1 year (TIMI)	2.79%
Major and minor bleeds at 1 year (TIMI)	4.56%
Minor bleeds at 1 year (estimated)	1.77%
% minor bleeds related to major bleeds	63%
Minor bleed 30 day (estimated)	Probability of major bleed at 30 days*63% = 0.41%
Minor bleed 1 year (estimated)	Probability of major bleed at 1 year*63% = 1.51%

It was deemed appropriate to use the major bleeding data when estimating rates for minor bleeding because the relationship between minor bleeding at 30 days and 1 year is likely to be similar for major bleeding at 30 days to 1 year. Table 16 shows the probabilities after calculations.

Table 16: Probabilities of major and minor bleeding

	Major bleed	Minor bleed
STEMI		
30 day	*0.94%*	*0.71%*
1 year	3.46%	2.61%
UA/NSTEMI		
30 day	0.65%	*0.41%*
1 year	2.38%	*1.51%*

Note: Values in italics indicate that they are calculated estimates.

As with the previous baseline risks, adjustments were made to obtain the correct number of events between 31 days and 1 year (r) and the total number of people at risk at 31 days (n) in order to calculate the correct probabilities of major or minor bleeding between 31 days and 1 year. These calculations are shown in Table 17 for major bleeding and Table 18 for minor bleeding.

Table 17: Data inputs for major bleeding baseline risk in STEMI and UA/NSTEMI

N	R	Probability	N	R	Probability
STEMI					
30 days			1 year		
3,752	35	0.94%	3,752	130	3.46%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		

N	R	Probability	N	R	Probability
3,752	35	0.94%	3,752 – (3,752*6.15%[a]) = 3,521	130 – 35 = 95	95/3,521 = 2.69%
UA/NSTEMI					
30 days			1 year		
2,617	17	0.65%	2,617	62	2.38%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
2,617	17	0.65%	2,617 – (2,617*1.79%[a]) = 2,570	62 – 17 = 45	45/2,570 = 1.77%

(a) This is the probability of death at 30 days, taken from Hulme 2019[16]

Table 18: Data inputs for minor bleeding baseline risk in STEMI and UA/NSTEMI

N	R	Probability	N	R	Probability
STEMI					
30 days			1 year		
3,752	27	0.71%	3,752	98	2.61%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
3,752	27	0.71%	3,752 – (3,752*6.15%[a]) = 3,521	98 – 27 = 71	71/3,521 = 2.03%
UA/NSTEMI					
30 days			1 year		
2,617	11	0.41%	2,617	40	1.51%
Recalculated for model inputs:					
0 to 30 days			31 days to 1 year		
2,617	11	0.41%	2,617 – (2,617*1.79%[a]) = 2,570	40 – 11 = 29	29/2,617 = 1.12%

(a) This is the probability of death at 30 days, taken from Hulme 2019[16]

2.3.8 Relative treatment effects in first year treatment period decision tree

Relative treatment effects for ticagrelor and prasugrel compared to clopidogrel were based on the systematic review of clinical evidence for clopidogrel, ticagrelor and prasugrel (in combination with aspirin) which was undertaken as part of guideline development. This is described in full along with the committee discussion of the clinical evidence in Evidence report A.

Note that the committee agreed that the best estimates of treatment effect to use for decision making in the guideline and so also in the model were from evidence syntheses that combined all ACS data together irrespective of ACS subtype (STEMI or UA/NSTEMI) or management approach (revascularisation or not). This was on the basis that the underlying mechanism is the same for all types of ACS and so it is reasonable to assume relative treatment effects may be similar and this maximises the evidence that contributes to the estimates of treatment effect. The committee discussed this issue in detail because there are also rational bases why relative treatment effects may vary between these groups. For example, STEMI is a medical emergency, requiring immediate treatment, so with well-established differential onsets of action of clopidogrel, prasugrel and ticagrelor, it is conceivable that this may impact their relative clinical effectiveness in STEMI patients. To

address this issue and ensure evidence suggesting any potential differential effects was not omitted, the committee reviewed the evidence for all ACS and also stratified by condition (i.e. STEMI or UA/NSTEMI) and management approach (i.e. with or without revascularisation) in pairwise meta-analyses. Following consideration of all the pairwise meta-analyses the committee concluded that it was reasonable to assume that relative treatment effects were consistent and that combined ACS population syntheses provided the best estimate of treatment effects for decision making purposes. Heterogeneity was not identified in the pairwise meta-analyses which suggests that the study populations did not differ in factors that interacted with the relative treatment effects. Following this an NMA was conducted for key 30 day outcomes using the overall ACS population to combine the available data for ticagrelor versus clopidogrel, prasugrel versus clopidogrel and ticagrelor versus prasugrel into a single set of consistent treatment effects using all available data to facilitate interpretation of the evidence and undertaking cost effectiveness analysis.

In the model relative treatment effects for prasugrel and ticagrelor compared to clopidogrel were applied to the baseline risks obtained for the clopidogrel arm in order to calculate revised risks of different clinical events with prasugrel and ticagrelor. As described in the previous section, baseline risks were specific to the population being evaluated in the model that is split by STEMI and UA/NSTEMI and for people receiving PCI. This means that while the relative treatment effects were not split by subgroup, because the baseline risks differed this resulted in different absolute effects. An example of how this works is demonstrated in Table 19.

Table 19: Example of absolute effect differences

	30 day probability of reinfarction with clopidogrel[(a)]	Number of people with reinfarction with clopidogrel per 1000	Odds ratio for ticagrelor	30 day probability with ticagrelor	Number of people with reinfarction with ticagrelor per 1000	Difference in number of people with reinfarction per 1000
STEMI	2.91%	29	0.81	2.03%	20	9
UA/ NSTEMI	1.02%	10		0.71%	7	3

(a) This is the baseline risk of reinfarction with clopidogrel

The odds ratios were applied to the baseline probabilities to obtain the probability of events occurring in the prasugrel and ticagrelor arms using the following formula:

$$probability\ in\ comparator\ arm = \frac{\exp(\ln(a) + \ln(b))}{1 + \exp(\ln(a) + \ln(b))}$$

- EXP = exponential
- a = odds of baseline probability
- b = odds ratio

0 to 30 days

The relative treatment effects applied in the model for the 0 to 30 day period are shown in Table 20. These were from a network meta-analysis that combined RCT evidence for ticagrelor versus clopidogrel (6 RCTs: PLATO[53], DISPERSE-2[6], Dehghani 2017[10], Wang 2019[55], Han 2019[15] and Jing 2016[17]), prasugrel versus clopidogrel (4 RCTs: TRITON-TIMI 38[28], ETAMI[61], TRILOGY[44] and Dasbiswas 2013[9]) and ticagrelor versus prasugrel (5 RCTs: PRAGUE18[29], RAPID I[42], RAPID II[41], Alexopoulous 2012[2] and Laine 2014[21]). Full methods for the NMA are described in the NMA report.

Table 20: Model inputs: relative treatment effects applied 0 to 30 days (from NMA)

Outcomes	Intervention	Odds ratio (95% CI) versus clopidogrel
All-cause mortality	Ticagrelor	0.84 (0.69 to1.02)
	Prasugrel	0.82 (0.64 to 1.03)
Reinfarction	Ticagrelor	0.69 (0.55 to 0.85)
	Prasugrel	0.79 (0.64 to 0.97)
Stroke	Ticagrelor	1.28 (0.86 to 1.83)
	Prasugrel	0.83 (0.45 to 1.39)
Major bleed	Ticagrelor	1.00 (0.89 to 1.11)
	Prasugrel	0.99 (0.61 to 1.52)
Minor bleed	Ticagrelor	1.18 (0.75 to 1.78)
	Prasugrel	0.74 (0.50 to 1.05)

Abbreviations: 95% CI = 95% confidence interval; NMA = network meta-analysis.

Source: Systematic review and NMA undertaken as part of guideline development. See Evidence report A and the NMA report for full methods. RCTs incorporated: ticagrelor versus clopidogrel, 6 RCTs (unpublished data obtained from authors for PLATO[53], DISPERSE-2[6], Dehghani 2017[10], Wang 2019[55], Han 2019[15] and Jing 2016[17]); prasugrel versus clopidogrel, 4 RCTs (STEMI subgroup from TRITON-TIMI 38[28], ETAMI[61], TRILOGY[44] and Dasbiswas 2013[9]); ticagrelor versus prasugrel, 5 RCTs (PRAGUE18[29], RAPID I[42], RAPID II[41], Alexopoulous 2012[2] and Laine 2014{Laine, 2014 #2631).

The network meta-analysis used simulation methods, which yielded 60,000 individual estimates of each odds ratio. These estimates represent the posterior distribution of the odds ratio. In the probabilistic economic analysis, for each iteration, we sampled at random from these 60,000 estimates. Each time we took both odds ratios (prasugrel vs clopidogrel and ticagrelor vs clopidogrel) from the same NMA iteration, to ensure that the correlation between the different treatment effects was preserved.

31 days to 1 year

The relative treatment effects applied in the model for the 31 day to 1 year period were obtained from the pairwise meta-analyses described in Evidence report A. The publication of ISAR-REACT 5 resulted in a data loop at 1 year for mortality, reinfarction, stroke and major bleeding (see Figure 4). An NMA for 1 year outcomes was explored, but the results were deemed unreliable due to inconsistency between direct and indirect treatment effects estimates. For example, the ticagrelor vs prasugrel estimate obtained from the ticagrelor vs clopidogrel and prasugrel vs clopidogrel studies was statistically different to that obtained from the ticagrelor vs prasugrel study (ISAR-REACT 5). The inconsistency was identified through conducting the Bucher test for inconsistency, which demonstrated that an NMA was not appropriate. Also, the studies and outcome data were all checked for accuracy. See the NMA report for results from the Bucher test. This was discussed with the committee and it was agreed that in order to utilise all sides of the network triangle, alternative scenarios for the base case model had to be conducted; it wasn't felt to be appropriate to select one set of data as the preferred data. Table 21 shows the relative treatment effects used in each of the alternative base case scenarios. The black text shows the trial data used in each scenario. The grey text indicates the implied odds ratios for the remaining comparison; this was calculated as a standard indirect comparison.

Figure 4: 1 year evidence network

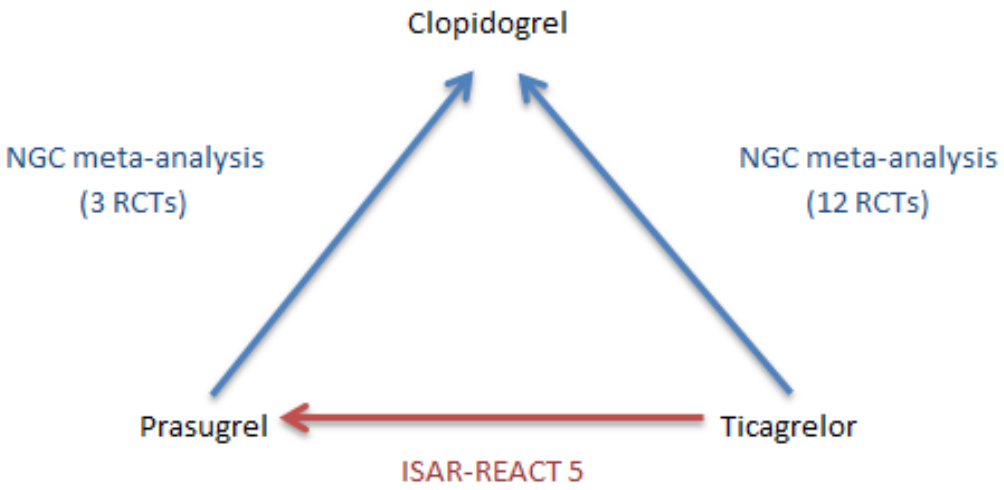


Table 21: Model inputs: relative treatment effects applied 31 days to 1 year (from pairwise meta-analysis)

	Scenario 1	Scenario 2	Scenario 3
Data used	Ticagrelor vs clopidogrel (meta-analysis) Prasugrel vs clopidogrel (meta-analysis) OR (95% CI)	Prasugrel vs clopidogrel (meta-analysis) Ticagrelor versus prasugrel (ISAR REACT 5) OR (95% CI)	Ticagrelor vs clopidogrel (meta-analysis) Ticagrelor versus prasugrel (ISAR REACT 5) OR (95% CI)
Ticagrelor vs clopidogrel			
All-cause mortality	0.77 (0.68 to 0.88)	1.24 (0.86 to 1.79)	0.77 (0.68 to 0.88)
Reinfarction	0.81 (0.72 to 0.92)	1.22 (1.54 to 3.07)	0.81 (0.72 to 0.92)
Stroke	1.13 (0.89 to 1.44)	1.08 (0.62 to 2.51)	1.13 (0.89 to 1.44)
Major bleed	1.04 (0.95 to 1.14)	1.52 (0.51 to 1.08)	1.04 (0.95 to 1.14)
Minor bleed	1.37 (1.19 to 1.57)[(a)]	1.37 (1.19 to 1.57)[(a)]	1.37 (1.19 to 1.57)
Prasugrel vs clopidogrel			
All-cause mortality	1.00 (0.83 to 1.21)	1.00 (0.83 to 1.21)	0.62 (0.44 to 0.87)
Reinfarction	0.75 (0.66 to 0.84)	0.75 (0.66 to 0.84)	0.50 (0.35 to 0.70)
Stroke	0.93 (0.67 to 1.30)	0.93 (0.67 to 1.30)	0.97 (0.50 to 1.88)
Major bleed	1.43 (1.14 to 1.79)	1.43 (1.14 to 1.79)	0.98 (0.71 to 1.35)
Minor bleed	2.07 (0.88 to 4.87)[(a)]	2.07 (0.88 to 4.87)[(a)]	2.07 (0.88 to 4.87)[(a)]
Ticagrelor vs prasugrel			
All-cause mortality	0.77 (0.61 to 0.97)	1.24 (0.90 to 1.70)	1.24 (0.90 to 1.70)
Reinfarction	1.08 (0.92 to 1.27)	1.63 (1.17 to 2.26)	1.63 (1.17 to 2.26)
Stroke	1.22 (0.80 to 1.84)	1.16 (0.62 to 2.14)	1.16 (0.62 to 2.14)
Major bleed	0.73 (0.57 to 0.93)	1.06 (0.78 to 1.44)	1.06 (0.78 to 1.44)
Minor bleed	0.66 (0.28 to 1.57)[(b)]	0.66 (0.28 to 1.57)[(b)]	0.66 (0.28 to 1.57)[(b)]

Abbreviations: 95% CI = 95% confidence interval; OR = odds ratio.

(a) ISAR-REACT 5 did not report minor bleeding therefore treatment effects remained the same as scenario 1.

(b) These estimates are the implied treatment effects for minor bleeding using the data for ticagrelor versus clopidogrel and prasugrel versus clopidogrel

Note: Black text shows the trial data used in each scenario; grey text is the implied treatment effect calculated from the trial data for other comparisons.

Source: Meta analyses of 1 year outcomes undertaken as part of guideline development. See Evidence report A for full methods. RCTs incorporated: ticagrelor versus clopidogrel, 12 RCTs (DISPERSE 2, Dehgani 2017[10], Han 2019[15], Li 2018[22], PHILO[13], PLATO[53], Tang 2016[51], Wang 2016[54], Wang 2019[55], Wu 2018[58], Yao 2017[60], Zhang 2016[62]); prasugrel to versus clopidogrel, 3 RCTs (Kitano 2019[19], Savonitto 2018[45], TRITON-TIMI[57]); ticagrelor versus prasugrel, 1 RCT (ISAR-REACT 5[46])

Note that treatment effects used were for 1 year outcomes rather than 31 days to 1 year. Ideally 30 day events would have been removed from the 1 year events and treatment effects recalculated however this was not possible in many cases as trials did not necessarily report both 30 day and 1 year outcomes. It was therefore agreed that 1 year relative treatment effects would be used. However, these treatment effects were applied to baseline risks that are specifically for 30 days to 1 year. The committee noted this limitation regarding the relative treatment effects but did not consider this to be a substantial issue.

Odds ratios were incorporated in to the probabilistic analysis using a log-normal distribution. This was parameterised using the mean odds ratio stated above and the standard error calculated from the confidence interval.

2.324 Transition probabilities in post-one year extrapolation Markov model

Differential treatment effects were assumed to apply in the first year only and so probabilities post one year do not vary by initial DAPT treatment.

The transition matrices showing the probabilities of transitions applied in the post-one year extrapolation Markov model for STEMI and UA/NSTEMI are shown in Table 22. Death is age-dependant and changes each cycle, therefore the probabilities of transitioning between the health states is dependent on this and changes every cycle.

Table 22: Post-one year extrapolation Markov model: transition matrices for STEMI and UA/NSTEMI excluding death

STEMI						
From	**To**					
	No further event	**Reinfarction**	**Post-reinfarction**	**Stroke**	**Post-stroke**	**Dead**
No further event	1 - 4.30% - 1.12% - age-dependant mortality	4.30%	0	1.12%	0	Age-dependant
Reinfarction	0	0	1 – age-dependant mortality	0	0	Age-dependant
Post-reinfarction	0	0	1 – age-dependant mortality	0	0	Age-dependant
Stroke	0	0	0	0	1 – age-dependant mortality	Age-dependant
Post-stroke	0	0	0	0	1 – age-dependant mortality	Age-dependant
Dead	0	0	0	0	0	1
UA/NSTEMI						
From	**To**					
	No further event	**Reinfarction**	**Post-reinfarction**	**Stroke**	**Post-stroke**	**Dead**
No further event	1 - 3.62% - 0.59% - age-dependant mortality	3.62%	0	0.59%	0	Age-dependant
Reinfarction	0	0	1 – age-dependant mortality	0	0	Age-dependant
Post-reinfarction	0	0	1 – age-dependant mortality	0	0	Age-dependant
Stroke	0	0	0	0	1 – age-dependant mortality	Age-dependant
Post-stroke	0	0	0	0	1 – age-dependant mortality	Age-dependant
Dead	0	0	0	0	0	1

In the post-1 year Markov model, people in the no further event health state had the possibility of transitioning to reinfarction, stroke or dead. The rate of reinfarction or stroke post 1 year was assumed to be the same as the rate for people on aspirin and clopidogrel between 31 days and 1 year. This is a method that has been employed by other models, for example, the previous model in NICE CG94 used the rate between 6 months and 1 year. The committee agreed that this was reasonable given that it excludes events occurring in the first 30 days (where events are more frequent) and as there was no data identified which provided the risk of reinfarction or stroke after 1 year in this population. The baseline risks that were used in the 1 year decision tree between 31 days and 1 year were used in the post year-one Markov model converted to a 1 year probability using standard formulae assuming a constant underlying rate. Also, the conversion accounted for censoring due to mortality.

In the model, reinfarction and stroke were tunnel health states, meaning that people only remain in that health state for one cycle, at which point they must transition to dead or the post-reinfarction/post-stroke health states; the probability of these transitions (excluding death) is therefore 1.

Once someone is in the post-reinfarction or post-stroke health state, they cannot experience another event and so either remain in that state or move to the dead state; the probability of remaining in these states (excluding death) is therefore 1.

Transition to the dead state

The transition probability of dying for each of the health states was determined by applying relevant standardised mortality ratios (SMRs) to cycle-specific general population mortality rates. This means that mortality rates increase with age in the model. These were then converted to probabilities using standard methods.

General population mortality was based on data from lifetables for England 2015-17.[39] Cycle-specific general population mortality was calculated taking into account the average age and gender split for the population entering the model and how this changed over time (age will increase by 1 year each cycle and mortality rate will increase with age; as mortality rates differ by gender and the average age by gender also varied in an ACS population, the gender split will change over time). Note that gender population mortality is not available beyond 100 years. Therefore, the model applies the mortality rate for age 100 to those that are older than 100 years. Table 23 shows age and gender split data used in the model. The percentage of people that are male and female that enter the Markov model was obtained from Hulme 2019. It is acknowledged that as the data obtained from Hulme 2019 was used to model mortality in the decision tree, this is the percentage split in the first year, therefore the percentage that are male and female after 1 year could be different. This was explored and showed that after accounting for mortality in the first year the percentage that were male and female remained the same, therefore the same values as reported in Hulme 2019 were used. The average age used in the Markov model to calculate mortality was one year higher than the reported age in the study, to reflect that people enter the Markov model one year after their ACS event.

Table 23: Model inputs: average age and gender split

Population	Model entry age	Male
STEMI	Male: 63 years Female: 70 years	75%
UA/NSTEMI	Male: 65 years Female: 70 years	72%

Source: Analysis of 2011/2012 PCI audit data for England and Wales by Hulme 2019.[16] Based on 41,974 PCIs for STEMI and 56,152 for UA/NSTEMI. Average start age was calculated from ages reported by gender and gender split reported in paper.

The model aimed to reflect the real-world population of people with ACS undergoing PCI in England. Data was therefore sought from reports of national audit data. Ideally we were looking for information specifically for people with ACS who have undergone PCI as demographics will be different to the overall ACS population and specific to STEMI and UA/NSTEMI separately as again demographics were considered to potentially vary by type of ACS. An analysis of national audit data in this format was identified in the study reported by Hulme 2019.[16] The data reported for the years 2011/2012 was used and included 40,724 PCIs for STEMI and 54,314 for UA/NSTEMI. More recent audit data is available however these demographics were not reported for these populations separately. It is noted however that for the overall PCI population (ACS and stable) these demographics are very similar in the most recent year and 2013/14.[25]

SMRs were identified from checking other models and published sources, and those used in the Markov model are shown in Table 24.

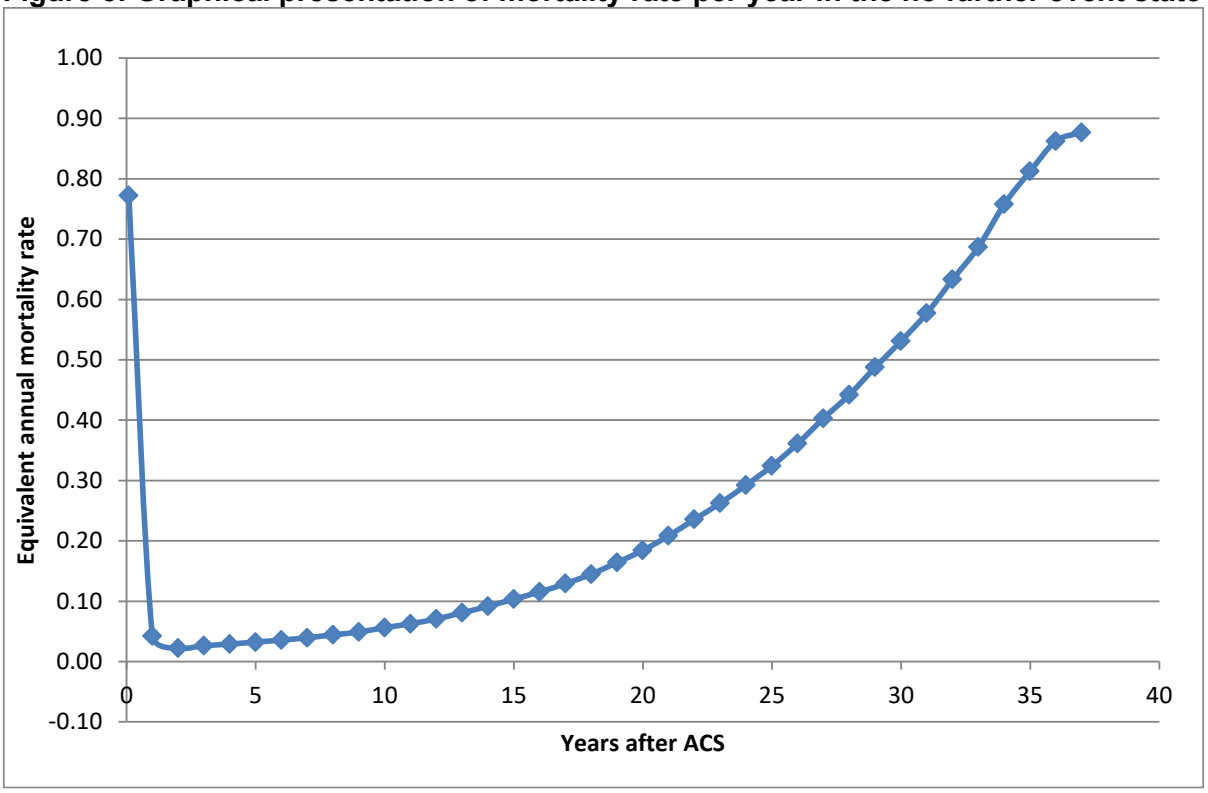
Table 24: Post-one year extrapolation Markov model: standardised mortality ratios

Event	SMR (95% CI)	Source
No further event	2.00 (1.99 to 2.01)[(a)]	Smolina 2012.[47] All-cause mortality compared to that expected in the general population after first acute MI. Based on individuals in England admitted to hospital between 2004 and 2010 (n = 371,619).
Reinfarction	4.50 (4.43 to 4.57)[(a)]	Smolina 2012.[47] All-cause mortality compared to that expected in the general population after second acute MI. Based on individuals in England admitted to hospital between 2004 and 2010 (n = 15,833).
Post-reinfarction	3.00 (2.95 to 3.05)[(a)])	
Stroke	4.73 (4.34 to 5.15)	Bronnum-Hansen 2001.[5] All-cause mortality after first non-fatal stroke compared to that expected in the general population in years 0-1 for males and females. Danish population 1982–1991 (n=8,324).
Post-stroke	2.37 (2.17 to 2.49)[(b)]	Bronnum-Hansen 2001.[5] Average of SMRs for years 1-15 for males and females. All-cause mortality after first non-fatal stroke compared to that expected in general population. Danish population 1982–1991 (n=8,324).

(a) CIs were not reported therefore these were calculated by assuming the standard deviation was equal to the mean and using the reported n number – n = 371,619 for first MI and n = 15,833 for second MI.
(b) CI's calculated from Monte Carlo simulation.

Figure 5 illustrates how mortality changes over time in the model for those in the no further event health state. The first two data points are the rates 0 to 30 days and 31 days to 1 year from the UK PCI audit data described in section 2.3.2. Data points after this are based on age and gender dependent general population mortality adjusted using the 'no further event' SMR in Table 24.

Figure 5: Graphical presentation of mortality rate per year in the no further event state



The SMR for the no further event and reinfarction/post-reinfarction health states were obtained from Smolina 2012.[47] This study reported long-term survival after a first and second acute MI in England in 387,452 individuals identified between 2004 and 2010. The SMRs were reported graphically and approximate average values for use in the model were obtained by visually assessing the graphs in discussion with clinical committee members. Also, the study reported that the SMR for those with their first MI stabilises at 2.00 by 4 years and for those with a second MI it stabilises at around 3.00 by 4 years. The study did not report confidence intervals (or information from which they could be calculated) and so they were estimated assuming the standard deviation was equal to the mean and the reported n number. The estimated confidence intervals are shown in Table 25.

Table 25: Estimates of confidence intervals for Smolina 2012[47] SMRs

Health state	Sample mean	Estimated standard deviation	Sample size	Estimated confidence intervals
No further event	2.00	2.00	371,619	1.99 to 2.01
Reinfarction	4.50	4.50	15,833	4.43 to 4.57
Post-reinfarction	3.00	3.00	15,833	2.95 to 3.05

The post-stroke standardised mortality ratios were obtained from Bronnum-Hansen 2001.[5] This study looked at long-term survival following a stroke in people in Denmark. The SMRs were reported separately for different time intervals, initially for years 0 – 1 and also for different intervals between years 2 – 15. To calculate the SMR for the post-stroke health state a straight average was used as the model reflects a lifetime perspective. A confidence interval for the average SMR was obtained using Monte Carlo simulation.

The SMRs were included in the probabilistic analysis using a lognormal distribution which was parameterised using the confidence intervals. General population mortality was not varied probabilistically.

2.3.5 Health-related quality of life

Health state weights (utilities)

Utilities were sought for the ACS population having dual-antiplatelet therapy who have experienced no additional event, reinfarction and stroke. Table 26 shows the data used in the model. These utilities were applied in both the first year treatment period decision tree and the post-year 1 Markov model.

When an event occurred in the decision tree, it was assumed this happened half way through the relevant time period, therefore, the utilities were applied as follows:

- For those having an event between 0 and 30 days, it was assumed to occur on average at 15 days (for example, no further event applied for 15 days and stroke applied for 15 days).
- For those having an event between 31 days and 1 year, it was assumed to occur on average after 5.5 months (not including the initial 30 day period) (for example, reinfarction for 5.5 months and dead for 5.5 months).

In the Markov model a half cycle correction was applied, which assumes that events occurred half way through the cycle (at 6 months).

Table 26: Model inputs: health state utilities

	Mean	SE
No further event	0.842	0.002
Reinfarction	0.779	0.010
Post-reinfarction	0.821	0.038
Stroke	0.703	0.010
Post-stroke	0.703	0.038

Abbreviations: SE = standard error

Source: NICE TA236 2011[38]. EQ-5D-3L completed by patients with ACS as part of PLATO health economic sub-study, UK valuation tariff applied.

Utilities were sought through checking cost-utility analyses identified in the systematic review of health economic studies in this area undertaken for this guideline update and recent NICE technology appraisals related to ACS. Additional ad-hoc searching was undertaken to establish if there was any more recent published data in the ACS population. The recent rivaroxaban NICE technology appraisal conducted a systematic review and concluded that the best available data was the utilities used in the ticagrelor NICE TA manufacturer model which were obtained from the PLATO health economics sub-study.[38] These were considered appropriate to use by the rivaroxaban TA evidence review group as they distinguished between those that have already had an ACS (no further event health state) and those that have reinfarction. The PLATO health economics sub-study administered the EQ-5D-3L to a subset of people in the RCT and the UK valuation set was used to obtain the utility weights. Although the manufacturer submission for the ticagrelor NICE TA used different utility values for the clopidogrel and ticagrelor arms, the ticagrelor TA evidence review group report indicated that this was not appropriate and that the same utilities should apply to each arm and the only difference in quality of life should be between which health state the person is in. The committee agreed that for this model the event specific utilities from the PLATO health economic sub study should be used as they match the health states in the model and are in line with the NICE reference case. It was agreed that quality of life should be lower in

the first year after having a reinfarction as this was considered clinically appropriate and is in line with other models in ACS.

It was acknowledged that in the decision tree those that have two events (e.g. stroke in 0 to 30 days and a stroke in 31 days to 1 year) may experience a further disutility. Although you may experience further disutility, it was agreed that the disutility associated with the second event would be smaller than the disutility associated with the first event. As a result, using the same utilities was considered a reasonable assumption by the committee.

The health state specific utility values were incorporated into the probabilistic analysis using a beta distribution, which is bounded by 0 and 1 as utilities are generally between these values. It is possible that utility values can be less than 1 (states considered worse than death) however given that the mean estimates for all of the health states are far from zero this was considered reasonable. This was parameterised using the method of moments approach that uses the mean and SE to calculate alpha and beta for the distribution.

Age adjustment of health state weights

Each year in the model utilities were age-adjusted in order to account for the fact that as people age their quality of life decreases. This is a method that is adopted by many other economic models and was also highlighted in the recent rivaroxaban NICE TA evidence review group report as being something that should be incorporated. If it is not done, QALYs may be overestimated.

Each year in the model age-specific general population EQ-5D-3L utilities were derived using the following formula from Ara 2010[3]:

$$Utility = 0.9508566 + 0.0212126 * Male - 0.0002587 * age - 0.0000332 * age\text{^}2$$

Note: for variable 'Male', male is equal to 1 and female is equal to 0.

The average age and gender split of the population was used in calculations as described in Table 23 in Section 2.3.4.

These were then combined with the health-state specific utilities using the multiplicative method.

Age-specific utilities were not varied probabilistically.

Bleeding adverse events

Minor bleeding and major bleeding (except stroke) were incorporated into the model as short term adverse events. The committee noted that you might expect a short term decrement in quality of life when experiencing a bleeding event and data was sought regarding this. The utility decrements applied for a minor and major bleed in the model along are shown in Table 27 along with the duration they were applied for in order to calculate QALY loss.

Table 27: Model inputs: minor and major bleeding quality of life decrements

Adverse event	Utility decrement[(a)] (95% CI)	Standard error[(b)]	Duration applied for[(c)]
Minor bleed	0.026 (-0.0470 to -0.0293)	0.005	7.60 days
Major bleed	0.038-(-0.0365 to -0.0148)	0.006	45.38 days

(a) Source: Amin 2016[16]. Primary analysis of EQ-5D-3L data (US tariff) from people with ACS on DAPT that experienced a bleed from the TRANSLATE-ACS study, n=9,290. Utility decrement was calculated in analysis by comparing quality of life of those who experienced a bleed to those who did not experience a bleed.
(b) Standard errors were calculated using the lower and upper 95% confidence intervals reported in the study
(c) Source: Doble 2018[12]

A systematic review conducted by Doble 2018[12] identified 12 studies that reported quality of life associated with major and minor bleeding for people taking DAPT. The study also conducted a small patient preference elicitation study using EQ-5D-3L and 5L to obtain utilities for major and minor bleeding. The elicitation exercise resulted in data collected from 21 individuals, who were all taking DAPT for ACS or after a coronary intervention. This study was conducted in the UK and used the EQ-5D-3L tariff which is line with NICE current preferred methods. The study reported that most participants completing the elicitation exercise had experienced a minor bleed; however, not everyone had experienced a major bleed. Due to the study being based on a small sample of people and the fact they were not directly affected by the condition, an alternative source that was identified in the systematic review was considered. The TRANSLATE-ACS study was a longitudinal study conducted in the USA looking at DAPT treatment patterns after an ACS event. The study was conducted in over 9,000 people that were treated with PCI and taking DAPT. Bleeding events were reported according to BARC and health related quality of life was recorded. Participant's EQ-5D scores were collected at baseline and 6 months. They reported utility decrements of people who experienced bleeding compared to those in the study that did not experience any bleeding. Although the study used the EQ-5D US tariff, it was felt appropriate to use this data over other studies as the study was conducted on a large number of people who were the population of interest. Although the US tariff was used, it uses the time-trade-off valuation method which is the same as the UK tariff. Also, the Doble 2018 study compared the US and UK valuation tariff in the elicitation exercise and showed that they resulted in small differences, which further supported the use of the values from the TRANSLATE-ACS study.

When applying utility decrements the duration that the event is expected to impact quality of life has to be applied. The TRANSLATE-ACS study did not report the duration that major and minor bleeds impacted quality of life, and the previous prasugrel NICE TA assumed that major bleeds would affect quality of life for 14 days. The Doble 2018 study asked participants in the elicitation exercise how long they would expect a bleed to impact quality of life and the average amount of time was 7.6 days for minor bleeds and 45.38 days for major bleeds. The committee agreed that this was the best source of data as it involved asking people on DAPT that may have experienced a bleed.

The utility decrement associated with major bleeding was incorporated into the probabilistic analysis using a gamma distribution. This is bounded by zero which reflects the assumption that this adverse events will only result in lower QALYs, which was agreed to be clinically appropriate. It was parameterised using the mean utility decrement and standard error calculated from the reported confidence interval.

The utility decrement with minor bleeding was incorporated into the probabilistic analysis using the difference in utility decrement with a minor bleed and a major bleed to ensure that in the probabilistic analysis the utility decrement with a minor bleed is not higher than with a major bleed. A gamma distribution was used for the difference for the same reasons as given above. It was parametrised using the difference in mean utility decrement and standard error calculated from the reported confidence intervals for the decrements for major and minor bleeding.

2.3.6 Resource use and costs

2.3.6.1 Intervention costs

In the analysis, DAPT costs varied by comparator in the first year. The unit costs of aspirin, clopidogrel, prasugrel and ticagrelor that are used in the model shown in Table 28. Clopidogrel, prasugrel and ticagrelor all require a loading dose to be used in people presenting with ACS. The loading dose for clopidogrel can either be 300mg or 600mg, but for the purposes of modelling the 600mg dose was used as this is what is often done in current practice. A sensitivity analysis using a 300mg loading dose was conducted as described in section 2.4. The daily dose of prasugrel is 10mg for adults 18 – 74 years and

with a body weight above 60kg, and for anyone under 60kg or 75 years and over the daily dose is 5mg. As the annual cost of the 5mg and 10mg dose is different, an assumption had to be made regarding what proportion of people would be receiving each dose. Recent prescription cost analysis data showed that 90% of prasugrel prescriptions were for the 10mg dose. However, as the current usage of prasugrel is low, this would not reflect the overall PCI population. As a result, a local hospital database was checked and showed that approximately 10 – 20% of people that have undergone PCI for ACS would be eligible for the 5mg dose. Therefore, the model assumed that 15% would receive the 5mg dose and 85% would receive the 10mg dose. All three drugs are taken alongside aspirin therefore the cost of aspirin was included. The doses and resulting costs of these drugs are shown in Table 29.

Table 28: DAPT unit costs

Drug	Tablet size	Tablets per pack	Cost per pack	Cost per tablet
Aspirin	75mg	28	£0.71	£0.03
Clopidogrel	75mg	28	£1.44	£0.05
Prasugrel	5mg	28	£28.84	£1.03
	10mg	28	£8.49	£0.30
Ticagrelor	90mg	56	£54.60	£0.98

(a) Source: British National Formulary[18], Accessed 7th February 2020

Table 29: Model inputs: DAPT costs

Drug	Loading dose	Loading dose cost	Daily maintenance dose	Cost per day	Cost per year
Aspirin	n/a	n/a	75mg	£0.03	£9.26
Clopidogrel	300mg	£0.20	75mg	£0.05	£18
	600mg	£0.40	75mg	£0.05	£18
Prasugrel	60mg	£1.82	5mg	£1.03	£376
			10mg	£0.30	£111
Ticagrelor	180mg	£1.95	180mg	£1.95	£712

Source: British National Formulary[18], Accessed 7th February 2020

Prasugrel can only be given in people undergoing PCI. Standard treatment for STEMI is primary PCI immediately. However management in people with UA/NSTEMI is different with a proportion of people undergoing angiography to determine if PCI is appropriate. It will not be known if these people will receive PCI until angiography has been undertaken and MINAP audit data showed that on average it takes around 3 days from event angiography (with some taking place sooner and some later). Therefore intervention costs in the UA/NSTEMI prasugrel group were calculated assuming that they would only receive aspirin for 3 days, and then receive the prasugrel loading dose on day 3 followed by daily prasugrel and aspirin costs. This was to be in line with what was conducted in the ISAR-REACT 5 trial. A sensitivity analysis was conducted which assumed that these people received clopidogrel until angiography and then were switched to prasugrel as the committee were uncertain about leaving people off DAPT until angiography.

Loading dose costs were applied to everyone in the model. The daily costs were then applied for 1 year apart from in those who died. For those that died between 0 to 30 days, the daily treatment costs were applied for 15 days. For those that died between 31 days and 1 year, the first 30 day intervention cost was applied and then the costs were applied for a further 5.5 months to be in line with the assumption that on average events occur half way through the cycle.

2.3.6.2 Health states

The sources of cost data for health states were identified by reviewing models in ACS and other cardiovascular models (NICE guidelines, TA models or published economic models) and through non-systematic online searches to identify newer publications. The costs applied in the model are summarised in Table 30 below. More detail about the data sources and calculation are provided in the sections that follow.

Note that in the year 1 decision tree, assuming events occurring between 31 days and 1 year occur around 6 months, costs were attributed assuming the first 6 month costs are determined by what occurs between 0 to 30 days and the second 6 months costs are determined by what event occurs during the 31 day to 1 year period.

Table 30: Model inputs: year 1 decision tree health state costs

0 to 30 days	31 day to 1 year	Cost	Source
No further event	No further event	£1,640	• Danese 2016[8]first MI 1 – 6 months costs with estimated acute cost removed (based on NHS reference cost of PCI[11]) • Plus half the Danese 2016[8] annualised post-6 months costs
No further event	Reinfarction	£5,564	• Danese 2016[8] first MI 1 – 6 months costs with estimated acute cost removed (based on NHS reference cost of PCI[11]) • Plus Danese 2016[8] second MI 1 – 6 months costs
No further event	Stroke	£15,203	• Danese 2016[8] first MI 1 – 6 months costs with estimated acute cost removed (based on NHS reference cost of PCI[11]) • Plus the Xu 2018[59] Year 1 stroke costs with recurrence costs removed , 6 month cost post-year 1cost removed, and non-publically funded social care costs removed
No further event	Death	£1,168	• Danese 2016[8] first MI 1 – 6 months costs with estimated acute cost removed (based on NHS reference cost of PCI[11])
Reinfarction	No new event	£5,104	• Danese 2016[8] second MI 1 – 6 months costs • Plus half the Danese 2016[8] annualised second MI post-6 months costs
Reinfarction	Reinfarction	£8,792	• Danese 2016[8] second MI 1 – 6 months costs multiplied by 2.
Reinfarction	Stroke	£18,431	• Danese 2016[8] second MI 1 – 6 months costs • Plus the Xu 2018[59] Year 1 stroke costs with recurrence costs removed, 6 month cost post-year 1cost removed, and non-publically funded social care costs removed
Reinfarction	Death	£4,396	• Danese 2016[8] second MI 1 – 6 months costs
Stroke	No new event	£17,323	• Xu 2018[59] Year 1 stroke costs with recurrence costs removed and non-publically funded social care costs removed.
Stroke	Reinfarction	£21,719	• Xu 2018[59] Year 1 stroke costs with recurrence costs removed and non-publically funded social care costs removed. • Plus Danese 2016[8] second MI 1 – 6 months costs

0 to 30 days	31 day to 1 year	Cost	Source
Stroke	Stroke	£21,014	• Xu 2018[59] Year 1 stroke costs with recurrence costs removed and non-publically funded social care costs removed. • Plus acute stroke costs estimated using method used in Xu 2018[59] and 2017/18 NHS reference costs
Stroke	Death	£14,035	• Xu 2018[59] Year 1 stroke costs with recurrence costs removed, 6 month cost post-year 1cost removed, and non-publically funded social care costs removed
Death	n/a	£0	Assumption

Stroke costs

The cost of stroke was based on Xu 2018[59] which estimated the financial burden of stroke to the NHS and social care services. This was done using a patient simulation based on UK Sentinel Stroke National Audit Programme data. The costs associated with stroke were estimated up to 5 years after the person incurred their first stroke. The costs of stroke were reported for 1 year and 5 years. Costs associated with the NHS and social care services were reported separately. The social care costs in the report included both publically funded and independently funded costs. Costs from this study are shown in Table 31.

Table 31: Costs from published sources: stroke

Health state	Cost	Source
Stroke 1 year	£23,052	Xu 2018 – SSNAP project inflated to 2017/18[59]
Stroke 5 year	£47,023	Xu 2018 – SSNAP project inflated to 2017/18[59]

Costs inflated from 2016 to 2017/18 using health services specific indices reported in the PSSRU publication Unit costs for health and social care; 2017/18 was the latest index available[7]

As this analysis takes an NHS and personal social services perspective, non-publically funded costs should not be included. A recent report published by the Stroke Association (Patel 2017[43]) used the assumption that approximately 50% of social care costs are publically funded. Therefore, an assumption was made in the model that 50% of these costs were publically funded, which was tested in a sensitivity analysis.

In the 1 year decision tree clinical events including stroke are modelled explicitly as you can have a stroke between 0 to 30 days and another between 31 days and 1 year. However, the Xu 2018 costs include repeat stroke events. The costs associated with recurrent strokes was based on unpublished data obtained from the authors and was recorded for the overall 5 year costs; therefore an adjustment was made to the 1 year costs. When someone experienced a second stroke in the model, the acute costs of stroke were calculated from NHS reference costs, using the same currency codes that were used in the SSNAP 2018 report[59] which involved non-elective stroke, thrombolysis, ambulance and scan costs. These are shown in Table 32. For those that experienced their first stroke in the 31 days to 1 year period, the cost of stroke was adjusted. Instead of halving the 1 year cost of stroke, it was deemed appropriate to assume that the majority of costs in the first year happen in the first 6 months. Therefore the annual cost of stroke after year 1 was halved and removed from the first year stroke cost to obtain a higher cost. This was done to ensure no costs were lost once people entered the Markov model in the post-stroke health state.

In the Markov model repeat events are not modelled explicitly and so it was deemed appropriate to use the Xu 2018 costs that captured the cost of repeat events.

Table 32: Cost of acute stroke

Currency Code	Currency Description	Activity	National average unit cost
Acute stroke admission			
Non-elective long stay			
AA35A	Stroke with CC Score 16+	12,203	£8,659
AA35B	Stroke with CC Score 13-15	14,461	£6,419
AA35C	Stroke with CC Score 10-12	17,864	£5,082
AA35D	Stroke with CC Score 7-9	20,624	£4,052
AA35E	Stroke with CC Score 4-6	20,118	£3,420
AA35F	Stroke with CC Score 0-3	12,652	£2,821
Non-elective short stay			
AA35A	Stroke with CC Score 16+	2,618	£951
AA35B	Stroke with CC Score 13-15	4,207	£736
AA35C	Stroke with CC Score 10-12	7,568	£730
AA35D	Stroke with CC Score 7-9	12,448	£712
AA35E	Stroke with CC Score 4-6	17,105	£683
AA35F	Stroke with CC Score 0-3	14,922	£667
Cost of admission for stroke (weighted average)			£3,310
Thrombolysis[a]			
YR23A	Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 5+	12	£719
YR23B	Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4	64	£959
Cost of thrombolysis (weighted average)			£921
Scan			
RD01A	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over	438,550	£131
RD20A	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	167,572	£79
Cost of scan (weighted average)[b]			£80
Ambulance			
ASS02	See and treat and convey	5,325,368	£252
Cost of ambulance[c]			£195
Total cost of acute stroke:			**£3,692**

Source: NHS Reference Costs 2017/18[11]

(a) Thrombolysis costs were based on day-case admissions, and assumed that 11.6% received thrombolysis as reported in SSNAP report

(b) Cost of scan was based on 98.1% of people having a CT scan and the remaining having an MRI, taken from SSNAP report

(c) This was based on 77.3% of people arriving by ambulance, taken from the SSNAP report

The stroke costs used in the model are summarised in Table 33.

Table 33: Costs used in the model: stroke

	Cost	Source/Assumptions
Decision tree		
Stroke occurring in 0 – 30 days	£17,323	Xu 2018[59] 1 year stroke cost removed recurrence costs and 50% of social care costs; based on unpublished data obtained from authors
Stroke 31 days to 1 year	£14,035	Xu 2018[59] 1 year stroke cost removed recurrence costs and 50% of social care costs as well as removed half the annualised cost (£3,288) to account for 6 months of ongoing treatment; based on unpublished data obtained from authors
Second stroke	£3,692	NHS reference costs 2017/18; based on the costs included in Xu 2018[59]
Markov model (annual costs)		
Stroke	£18,522	Xu 2018[59] 1 year costs with 50% of social care costs removed
Post-stroke	£6,576	Xu 2018[59] 5 year costs adjusted to remove 1 year cost and annualised; 50% of social care costs removed.

ACS with no further event and ACS with new MI costs

Danese 2016[8] aimed to illustrate the costs to the NHS that are associated with cardiovascular events among adults receiving lipid modifying therapy. This was a retrospective cohort study that used Clinical Practice Research Datalink records from 2006 to 2012. They reported the costs to the NHS associated with having a myocardial infarction. The study recorded first events and repeat events, and the costs were reported separately for these. Costs were reported for the first six months following the acute event, and the cost incurred from 7 to 36 months was presented as an annualised cost. Costs from this study are shown in Table 34.

It was acknowledged that the cost used in the model for people with ACS (MI or unstable angina) but no further event is based on people who have had a myocardial infarction only; however the committee agreed that the downstream resource use and management strategy would be similar for this population especially as this analysis considered people with ACS undergoing PCI.

It was discussed that this study was based on people receiving lipid modifying therapy prior to the cardiovascular event they experienced. However, the committee indicated whether you are taking lipid modifying treatment before an event should not impact the treatment you receive for having a myocardial infarction and therefore these costs could be applied in this model.

Table 34: Costs from published sources: ACS with and without new MI

Health state	Cost	Source
First MI 1 – 6 months	£4,370	Danese 2016 inflated to 2017/18[8]
First MI post-acute annual cost	£943	Danese 2016 inflated to 2017/18[8]
Second MI 1 – 6 months	£4,396	Danese 2016 inflated to 2017/18[8]
Second MI post-acute annual cost	£1,415	Danese 2016 inflated to 2017/18[8]

Costs inflated from 2014 to 2017/18 using health services specific indices reported in the PSSRU publication Unit costs for health and social care; 2017/18 was the latest index available[7]

For those that experienced no further event in the model (that is people who have had an ACS but no further event), the cost of having a first MI was applied. For those that had reinfarction in the model, the cost of second MI was applied. In the decision tree it was decided that the cost of the acute event (hospitalisation) should be removed from the initial 6 month cost as everyone in the model experiences an ACS. Danese 2016 did not report a breakdown of the costs in order to remove this acute cost. As a result, the cost of having PCI was obtained from NHS reference costs and this was removed from the overall cost. The NHS reference costs of PCI are shown in Table 35.

Table 35: NHS reference costs 2017/18 of percutaneous coronary angioplasty

Currency Code	Currency Description	Number of FCE's	National average unit cost
Non-elective long stay			
EY40A	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	752	£7,572
EY40B	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	1,335	£5,447
EY40C	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	3,165	£4,485
EY40D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	3,061	£3,969
EY41A	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	1,307	£6,826
EY41B	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	2,802	£4,577
EY41C	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	9,037	£3,649
EY41D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	10,510	£3,185
Non-elective short stay			
EY40A	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	292	£3,152
EY40B	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	476	£2,346
EY40C	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	1,579	£2,228
EY40D	Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	2,236	£2,224
EY41A	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+	427	£2,507
EY41B	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11	1,127	£1,963
EY41C	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7	5,137	£1,884
EY41D	Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3	8,843	£1,784
Weighted average cost (used as acute cost of MI)			**£3,202**

Abbreviations: FCE = finished consultant episode
Source: NHS Reference Costs, 2017/18[11]*; cost of non-elective long stay includes excess bed day cost*

The costs used in the model for people with ACS without any event and with a reinfarction are summarised in Table 36.

Table 36: Costs used in the model: ACS with and without reinfarction

	Cost	Source/Assumptions
Decision tree		
ACS no further event (0-6 month cost)	£1,263	Danese 2016 first MI 1 – 6 months with acute cost removed (based on NHS reference cost of PCI)
ACS no further event (6 to 12 months cost)	£471	Danese 2016 first MI annualised post-acute event cost halved
Second MI (0 to 6 month cost)	£4,396	Danese 2016 second MI 1 – 6 months
Second MI (6 to 12 months cost)	£708	Danese 2016 second MI annualised post-acute event cost halved
Third infarction	£4,396	Danese 2016 second MI 1 – 6 months
Markov health state costs		
No further event	£943	Danese 2016 first MI annualised post-acute event cost
Reinfarction	£5,104	Danese 2016 second MI acute cost (1 – 6 months) and annualised post-acute event cost halved
Post-reinfarction	£1,415	Danese 2016 second MI annualised post-acute event cost

Source: Danese 2016[8]

Deaths occurring between 0 and 30 days costs

For those that died at 0 to 30 days, no health state costs were included as the cost associated with 15 days would be minimal.

2.3.63 Adverse events

Major and minor bleeding was incorporated in the model as adverse events. The costs associated with these events were applied as a one off. Previous models in ACS and especially DAPT were explored to see how the cost of bleeding was captured. Various approaches were taken and there was a large difference in the costs used in previous models. It was considered by the committee that these costs can vary from person to person as both minor and major bleeds can vary in severity.

Minor bleeding

Although the committee noted that minor bleeds usually don't require interventions, people experiencing a minor bleed may feel worried about the bleed and still seek medical help. As a result, it was considered reasonable to use an A&E visit with investigation. An average of NHS reference costs for all categories of emergency admission (weighted by number of attendances) was used; this is shown in Table 37.

Table 37: Minor bleeding cost based on emergency medicine admission

Currency codes	Currency descriptions	Total attendances	Weighted average cost used in model
VB01Z – VB09Z	Emergency Medicine, Category 1 - 3 Investigation and Emergency Medicine, Any Investigation	16,250,140	£176

Source: NHS Reference Costs 2017/18[11]

The NICE TA for long term ticagrelor use (TA420) used a much higher cost for minor bleeds which was based on an admission for gastrointestinal bleed without intervention. As a result of such differences in costs, this was used in a sensitivity analysis (described in section 2.4).

Major bleeding

It was discussed that major bleeding can include intracranial bleeds; however gastrointestinal bleeds are more common in this population taking DAPT. As a result, the average cost of an admission for gastrointestinal bleed was used in the base case analysis. An average of NHS reference costs for all categories of gastrointestinal bleed admission (weighted by number of attendances) was used; this is shown in Table 38 and how it was derived. In a sensitivity analysis the costs of intracranial bleeds were included (described in section 2.4).

Table 38: Major bleeding costs based on gastrointestinal bleed

Currency code	Currency description	Number of FCE's	National average unit cost
Non-elective long stay			
FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	1,058	£5,685
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	955	£3,637
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	1,486	£3,909
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	2,244	£2,828
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	5,568	£2,173
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	2,499	£2,920
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	6,754	£2,246
Non-elective short stay			
FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	32	£1,511
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	25	£1,130
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	69	£1,219
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	101	£1,047
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	202	£1,069
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	1,962	£586
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	9,160	£538
Weighted average			**£1,955**

Abbreviations: CC = complication and comorbidity; FCE = finished consultant episode
Source: NHS Reference Costs 2017/18[11]*; non-elective long stay costs including excess bed day costs*

2.4 Sensitivity analyses

2.4.1 Stroke 1 year baseline risk adjusted (SA1)

In the base case analysis 1 year baseline risk for stroke was estimated using 30 day stroke risk form UK audits and the percentage increase in events at 1 year compared to 30 days from the Swedeheart audits for STEMI and NSTEMI.[49, 50] The percentage increase to 1 year relative to 30 days was much lower with the PLATO data.[52] Therefore, an analysis was undertaken where the baseline risk for 1 year was determined by the percentage increase from PLATO. Table 39 shows the values used in the base case analysis and the values used in the sensitivity analysis.

Table 39: Baseline probability of stroke at 1 year

Population	30 day probability of stroke	% increase used in base case	1 year probability of stroke used in base case	% increase used in sensitivity analysis	1 year probability used in sensitivity analysis
STEMI	0.30%	420%(a)	1.25%	224%(c)	0.72%
UA/NSTEMI	0.11%	580%(b)	0.63%	224%(c)	0.26%

(a) Source: Szummer 2017; based on Swedeheart registry[49]
(b) Source: Szummer 2018; based on Swedeheart registry[50]
(c) Source: Wallentin 2009; based on PLATO RCT[52]

2.4.2 Rivaroxaban treatment effects included (SA2)

As discussed in section 2.1.1, there is an existing NICE technology appraisal (TA335) which recommends rivaroxaban as an option in combination with aspirin plus clopidogrel in people who have had an acute coronary syndrome post-acute management. If a recommendation to use prasugrel or ticagrelor is made, then the use of rivaroxaban in this scenario will be inappropriate as it is not licensed for use alongside these other antiplatelets. While the use of rivaroxaban for this indication was beyond the scope of this guideline update, the committee felt it was relevant to consider whether the use of rivaroxaban in people who received clopidogrel would affect conclusions about which DAPT option was preferred. Therefore an exploratory analysis was undertaken where treatment effects of rivaroxaban were incorporated into the model in order to see if this would impact results.

Table 40: Relative treatment effects of rivaroxaban plus clopidogrel

Outcome	Hazard ratio (95% CI) versus clopidogrel
Mortality	0.83 (0.72 to 0.97)
Reinfarction	0.90 (0.75 to 1.09)
Stroke	1.13 (0.74 to 1.73)
Major bleed	3.46 (2.08 to 5.77)
Minor bleed	1.62 (0.92 to 2.82)

(a) Source: ATLAS-TIMI-51 RCT[27]

Treatment effects were obtained from the ATLAS-TIMI-51 trial.[27] These are shown in Table 40. An issue with this study was that hazard ratios were reported at 24 months, which was not in line with the outcomes from our clinical review, which reported outcomes at 30 days and 1 year. In order to undertake the sensitivity analysis an assumption was made to assume that treatment effects remain constant. It was highlighted that the distribution of effects is probably not the same throughout 24 months, for example, bleeding events may be more likely in the first few months, however this was an assumption that was made in the absence of other data. Hazard ratios were used as they were reported by the study. They were applied to the events rates 0 to 30 days and 31 days to 1 year with clopidogrel and

aspirin in the model and revised probabilities of events occurring were obtained. These are shown in Table 41. The unit costs of the drugs used in this analysis are presented in Table 42.

Table 41: Probability of events in rivaroxaban and clopidogrel arm

Outcome	Probability at 30 days	Probability at 1 year
STEMI		
All-cause mortality	5.13%	3.16%
Reinfarction	2.63%	3.50%
Stroke	0.34%	1.14%
Major bleed	3.21%	9.01%
Minor bleed	1.14%	3.27%
UA/NSTEMI		
All-cause mortality	1.49%	3.09%
Reinfarction	0.92%	2.94%
Stroke	0.12%	0.60%
Major bleed	2.21%	5.98%
Minor bleed	0.66%	1.81%

Table 42: Unit costs of drugs

Drug	Tablet size	Tablets per pack	Cost per pack	Cost per tablet
Aspirin	75mg	28	£0.71	£0.03
Clopidogrel	75mg	28	£1.40	£0.05
Rivaroxaban	2.5mg	56	£50.40	£0.90

Source: British National Formulary[18]; accessed 30th August 2019

2.4.3 Utilities not age-adjusted (SA3)

In the base case analysis the utility values were age-adjusted in order to account for the fact that as people age their quality of life decreases. Although this is a method that is deemed appropriate and was recommended by the evidence review group report for the rivaroxaban NICE TA, a sensitivity analysis was conducted where the utility values were not adjusted. This was conducted for methodological reasons to test if utilities impacted conclusions. Instead, the values from Bagust 2011 were used for each year the person was alive, based on the health state they were in. Table 43 shows the mean values applied.

Table 43: Utility values from Bagust 2011

	Mean	SE
No further event	0.842	0.002
Reinfarction	0.779	0.010
Post-reinfarction	0.821	0.038
Stroke	0.703	0.010
Post-stroke	0.703	0.038

2.4.4 Dyspnoea included in the analysis (SA4)

As discussed in section 2.2.1, the committee highlighted that a considerable amount of people taking ticagrelor will experience breathing difficulties as a side effect. Although this wasn't considered a critical outcome to include in the base case analysis, it was incorporated as part of a sensitivity analysis to test if this impacted conclusions. Real world estimates of baseline risks for dyspnoea were not available for the clopidogrel arm; therefore the

estimates from the clinical review were used in order to obtain the probability of experiencing dyspnoea on clopidogrel. The treatment effects were also obtained from the clinical review (Evidence report A), and both the baseline risk and treatment effect are shown in Table 44. There was no data comparing dyspnoea for prasugrel versus clopidogrel, and only 1 study comparing prasugrel and ticagrelor reported dyspnoea; however this was based on a small number of participants and at an unspecified time point. Therefore, it was assumed that the rates for prasugrel were the same as clopidogrel, and this was considered an appropriate assumption by the committee.

Table 44: Dyspnoea baseline risks and treatment effects

Time point	Baseline risk with clopidogrel(a)	Treatment effect with ticagrelor (OR, 95% CI)(a)
STEMI		
30 days	5.10%	2.39 (1.09 to 5.27)
1 year	8.27%	1.77 (1.62 to 1.93)
UA/NSTEMI		
30 days	5.10%	2.39 (1.09 to 5.27)
1 year	7.90%	1.77 (1.62 to 1.93)

Abbreviations: 95% CI = 95% confidence interval; OR = odds ratio
(a) Source: Systematic review and meta analyses undertaken as part of guideline (see Evidence report A)

The committee discussed the impact that experiencing breathing difficulties would have on the adult, and it was agreed that some people might discontinue their antiplatelet. However, it was agreed that discontinuation would not be incorporated for modelling purposes. The committee indicated that a small number of people would stop taking ticagrelor or be swapped to another antiplatelet, and it was discussed that the impact this would have on the treatment effects would be captured. It was also discussed that people will be informed of this side effect, therefore not everyone will seek medical help. However, a proportion of people may see their GP and the committee discussed that this could lead to a range of different management strategies such as requiring blood tests or an asthma review. Therefore, these resource implications had to be captured. For modelling purposes it was agreed to assume that 80% of people experiencing dyspnoea will see their GP, and 30% will have investigative tests conducted by nurse. The costs used are demonstrated in Table 45.

Table 45: Resource use associated with dyspnoea

Appointment	Cost	Cost adjusted
General practitioner	£37 (per 9.22 minutes)	n/a
Nurse (GP practice)	£42 (per hour)	£14 (per 20 minutes)
Total cost per person		**£34**

Source: PSSRU unit costs 2018[7]; assumption that 80% of people would see their GP and 30% will have investigative tests with a nurse.

2.4.5 Bleeding costs (SA5 – 10)

As discussed in section 2.3.6.3, the costs associated with bleeding can vary and previous technology appraisals have used different estimates. Therefore, different estimates were used to explore whether this impacted results. Firstly, the cost of minor bleeding was adjusted to include the cost of a gastrointestinal bleed without interventions, which was the method adopted by the ticagrelor technology appraisal, and is much higher than the cost used in the base case. Also, the committee noted that a large proportion of bleeds would be gastrointestinal; therefore a sensitivity analysis using this cost was considered appropriate. This cost was obtained from NHS Reference Costs and is shown in Table 46.

Table 46: Cost of minor bleed for sensitivity analysis (SA5)

Currency code	Currency description	Number of FCE's	National average unit cost
Non-elective long stay			
FD03H	Gastrointestinal Bleed without Interventions, with CC Score 0-4	15,230	£1,699
Non-elective short stay			
FD03H	Gastrointestinal Bleed without Interventions, with CC Score 0-4	40,952	£448
Weighted average			**£731**

Abbreviations: FCE = finished consultant episode
Source: NHS reference costs 2017/18[11]; non-elective long stay cost includes the cost of excess bed days

The cost of major bleeding was varied, in order to capture the cost of intracranial bleeds. The committee highlighted that gastrointestinal bleeds were more prominent in those taking DAPT, therefore the proportion of major bleeds that were intracranial was tested and set to 10%, 20%, 30% and 40%. These costs were obtained from NHS Reference Costs and are shown in Table 47. The change in the cost of a major bleed applied in the analysis is demonstrated in Table 48.

Table 47: Cost of intracranial bleeds

Currency code	Currency description	Number of FCE's	National average unit cost
Non-elective long stay			
AA23C	Haemorrhagic Cerebrovascular Disorders with CC Score 14+	1,224	£7,666
AA23D	Haemorrhagic Cerebrovascular Disorders with CC Score 10-13	1,541	£4,899
AA23E	Haemorrhagic Cerebrovascular Disorders with CC Score 6-9	2,160	£3,957
AA23F	Haemorrhagic Cerebrovascular Disorders with CC Score 3-5	1,522	£3,503
AA23G	Haemorrhagic Cerebrovascular Disorders with CC Score 0-2	994	£3,226
Non-elective short stay			
AA23C	Haemorrhagic Cerebrovascular Disorders with CC Score 14+	344	£1,038
AA23D	Haemorrhagic Cerebrovascular Disorders with CC Score 10-13	777	£778
AA23E	Haemorrhagic Cerebrovascular Disorders with CC Score 6-9	1,668	£777
AA23F	Haemorrhagic Cerebrovascular Disorders with CC Score 3-5	1,755	£809
AA23G	Haemorrhagic Cerebrovascular Disorders with CC Score 0-2	1,471	£776
Weighted average			**£2,625**

Abbreviations: FCE = finished consultant episode
Source: NHS reference costs 2017/18[11]; non-elective long stay costs include the cost of excess bed days

Table 48: Costs used in major bleeding sensitivity analyses

Sensitivity analysis	Proportion of major bleeds that are intracranial	Cost used in model
SA6	10%	£2,048
SA7	20%	£2,141
SA8	30%	£2,234
SA9	40%	£2,327

Lastly, a sensitivity analysis was conducted where both the cost of minor bleeds and major bleeds were adjusted (SA10). This involved using the higher cost of gastrointestinal bleeds for minor bleeds and the assumption that 20% of major bleeds would be intracranial, and these were adjusted simultaneously to see if this impacted results.

2.4.16 Proportion of stroke social care costs that are publically funded (SA11 – 12)

As described in section 2.3.6.2 the proportion of stroke social care costs that were publically funded was assumed to be 50%, which was in line with a previous assumption from a published report. This was tested in a sensitivity analysis, by changing the proportion of social care costs that were publically funded to 70% (SA11) and 30% (SA12), to see if this impacted conclusions on cost-effectiveness.

2.4.17 Clopidogrel loading dose set to 300mg (SA13)

The base case model uses a clopidogrel loading dose of 600mg for costing purposes. However, it is noted that some people may only receive a 300mg loading dose, therefore this was incorporated as a sensitivity analysis to see if this impacted conclusions.

2.4.18 Assuming no treatment effect with stroke (SA14 – 16)

There was ambiguity around including the stroke outcome in the model as the committee discussed that it affected small numbers and there was uncertainty in the treatment effect estimates. Stroke has high costs associated with it therefore a small number of people experiencing strokes can have a large impact in results. As a result a sensitivity analysis was conducted where there was no treatment effect applied for prasugrel and ticagrelor (by changing the treatment effect to 1) to see if this impacted results (SA14). Also, a sensitivity analysis was conducted where there was no stroke treatment effect applied for ticagrelor but it was still applied for prasugrel (SA15) and another analysis where the stroke treatment effect for prasugrel was not applied but ticagrelor's treatment effect was still applied (SA16).

2.4.19 UA/NSTEMI prasugrel arm loading dose (SA17)

In the base case analysis it was assumed that the UA/NSTEMI prasugrel arm would not receive any dual antiplatelet therapy until the decision to undergo PCI was made. This resulted in the model only applying the cost of aspirin for the first 3 days and then a loading dose of prasugrel on day 3, followed by prasugrel for the rest of the duration. This was conducted to be in line with the ISAR-REACT 5 trial. It was discussed that there may be situations in real practice where the patient has already started another antiplatelet, therefore a sensitivity analysis was conducted where a 600mg clopidogrel loading dose was given on day 1 and clopidogrel and aspirin was costed for 3 days, and then they switched to prasugrel and the cost of prasugrel was accounted for beyond 3 days.

2.4.10 Reducing SMRs for ACS/Reinfarction (SA18)

The SMRs being used for the no further event, reinfarction and post-reinfarction health states were obtained from Smolina 2012[47] and the SMRs for stroke and post-stroke were obtained from Bronnum-Hansen 2001.[5] As the SMRs were obtained from alternative sources, there is a chance that the SMRs related to ACS and reinfarction may be overestimating death. This is because they will comprise of deaths from any cause, and therefore would include death from having a stroke. In order to account for this, a sensitivity analysis was conducted where the SMRs for no further event, reinfarction and post reinfarction were reduced by 20% to reduce mortality in these health states and to test if this impacts results.

2.4.11 Adjusting baseline risks for reinfarction and stroke (SA19)

As discussed in section 2.3.2, some of the probabilities used in the decision tree may overestimate the number of people alive with MI or stroke at 1 year. The data for reinfarction with STEMI included all events (not just people alive with reinfarction at 30 days and 1 year), as well as the stroke data for both STEMI and UA/NSTEMI. It was discussed that this would overestimate the number of people alive with a reinfarction and stroke and therefore a sensitivity analysis was conducted to reduce these probabilities at 1 year. In order to obtain a good estimate of how many of these events would be fatal, data from the ticagrelor TA236[38] was used as it provided a breakdown of events for the clopidogrel arm, which showed that 18% of people that had a reinfarction had died at the end of 1 year, and 20% of people that had a stroke had died at the end of 1 year. Therefore, the 1 year probability for reinfarction in STEMI was reduced by 18% and the 1 year probability for stroke was reduced by 20% for both STEMI and UA/NSTEMI. Reinfarction for UA/NSTEMI remained unchanged as it was the probability for non-fatal events.

2.4.12 Discount rate (SA20)

In-line with NICE methodological guidance a sensitivity analysis was undertaken where the discount rate was set to 1.5% for costs and outcomes instead of 3.5% to explore whether results were sensitive to the discount rate used.

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 started in the decision tree in the ‘no further event’ health state. People moved to the other health states (reinfarction, stroke and dead) based on probabilities of events occurring which was calculated from baseline risks and treatment effects. Those alive at the end of the decision tree at year 1 entered the Markov model and started in cycle 0. The health state they entered was determined by which health state they were in at the end of year 1 in the decision tree. Those that experienced no further event at the end of year 1 entered the ‘no further event’ health state in the Markov model. Those that had a reinfarction (once or twice) entered the ‘post-reinfarction’ health state in the Markov model. Those that had a stroke entered the ‘post-stroke’ health state in the Markov model. Once entering the Markov model, transition probabilities from the ‘no further event’ health state to ‘reinfarction’ and ‘stroke’ were based on the baseline risks at 1 year in the decision tree. Mortality transition probabilities varied depending on age, sex and which health state they were in.

Standardised mortality ratios for each health state were applied to mortality rates; which were then converted into transition probabilities for the respective cycle length (1 year) before inputting into the Markov model. These were converted using the following formulae:

$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 year)

To calculate QALYs for each cycle life years were weighted by a utility value (this was not treatment dependent). A half-cycle correction was applied, assuming that people transitioned between states on average halfway through a cycle. QALYs were then discounted at 3.5% to reflect time preference. QALYs during the first cycle (in the decision tree) were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle were calculated on the same basis as QALYs and were discounted at 3.5% to reflect time preference. Each of the health states had specific costs applied.

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 cost and QALYs accrued by each cohort (STEMI and UA/NSTEMI) was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

2.6 Model validation

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

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. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations. The model was also peer reviewed by a health economist at NICE and an executable version of the model with full technical report was made available to registered stakeholders for review at consultation.

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 then options 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.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy.

2.8 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[36] 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.

3 Results

3.1 Base case

Base case analysis results are presented in Table 49 and shown graphically in Figure 6. In addition, scatter plots showing the distribution of cost and QALY pairs from the probabilistic analysis are shown in Figure 7 to Figure 9. Breakdowns of clinical events and costs are presented in Table 50 and Table 51.

As described in the methods (see section 2.3.3), base case results are presented for three scenarios that utilise different data to inform the relative treatment effects between 30 days and 1 year in the model (all scenarios use the 30-day NMA to inform the relative treatment effects 0 to 30 days in the model):

1. Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)
2. Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)
3. Ticagrelor vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)

In the base case analysis, the DAPT option that was most cost effective depended on the clinical data used to inform relative treatment effects between 31 days and 1 year and the ACS subpopulation. Prasugrel was the most cost effective DAPT option except in a UA/NSTEMI population when data from studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel was used to inform the relative treatment effects between 30 days and 1 year in the model (data scenario 1). In addition, although prasugrel was overall the most cost effective option in a STEMI population in scenario 1, there was a lot of uncertainty between whether prasugrel or ticagrelor was the most cost effective option, with prasugrel only being the most cost effective option in 53% of simulations and ticagrelor in 47%. Also, although ticagrelor was the most cost effective option for UA/NSTEMI in scenario 1, there was some degree of uncertainty as it was only the most cost effective option in 63% of simulations. There was however little uncertainty that prasugrel was the most cost-effective option in data scenarios 2 and 3 that utilise the recent ISAR-REACT 5 RCT comparing prasugrel and ticagrelor to inform the relative treatment effects between 31 days and 1 year in the model. Ticagrelor had the highest costs in all scenarios and ACS subgroups but only had the highest QALYs in scenario 1. In scenarios 2 and 3, prasugrel had lower costs than ticagrelor and higher QALYs. Clopidogrel had the lowest costs in all scenarios and had the lowest QALYs in all scenarios for STEMI and scenarios 1 and 3 for UA/NSTEMI.

The results in scenario 2 favoured clopidogrel over ticagrelor, and this was due to the treatment effects between 31 days and 1 year for ticagrelor versus clopidogrel being inferred by the prasugrel versus clopidogrel arm and the ticagrelor versus prasugrel arm. As ticagrelor was inferior to prasugrel in the ISAR-REACT 5 trial and prasugrel was superior to clopidogrel in the meta-analysis, this resulted in the inferred treatment effects suggesting that ticagrelor was worse than clopidogrel.

In all scenarios the main driver of the higher costs with ticagrelor and lower costs with clopidogrel was the intervention costs, as the intervention costs associated with ticagrelor was over £600 more than clopidogrel for both STEMI and UA/NSTEMI. As prasugrel had the second highest intervention costs, this resulted in prasugrel having the second highest lifetime costs.

In scenario 1 the results for STEMI and UA/NSTEMI showed different conclusions, with prasugrel being the most cost effective for STEMI and ticagrelor being the most cost-effective option for UA/NSTEMI. In both populations ticagrelor had the highest costs and QALYs but it was only cost effective compared to prasugrel in the STEMI population. The reason for this difference in results is largely attributable to the baseline risks. The STEMI population had a smaller incremental QALY gain between ticagrelor and prasugrel compared

to UA/NSTEMI. The reason for this difference was due to the mortality in the first year. Because STEMI had a higher baseline risk of death in 0 to 30 days, the absolute effect was greater for ticagrelor and prasugrel, with prasugrel having less deaths due to having a slightly better odds ratio (0.81 for prasugrel and 0.85 for ticagrelor). This resulted in 50 deaths with prasugrel compared to 53 with ticagrelor. This difference was offset by the events in 31 days to 1 year because the odds ratio was worse for prasugrel (1.00 for prasugrel and 0.77 for ticagrelor). Therefore, ticagrelor had 28 deaths compared to 36 with prasugrel. This resulted in ticagrelor having less deaths overall in the first year, but the difference was relatively small. In the UA/NSTEMI population, the absolute effect was smaller in 0 to 30 days as the baseline risk was smaller, and prasugrel and ticagrelor both resulted in 15 deaths. Between 31 days to 1 year, ticagrelor resulted in 28 deaths and prasugrel had 37 deaths (as the odds ratio for mortality was better for ticagrelor). Therefore, ticagrelor resulted in 3 less deaths compared to prasugrel for STEMI and 9 less deaths for UA/NSTEMI, and this larger difference in the UA/NSTEMI population is what drove larger QALY differences.

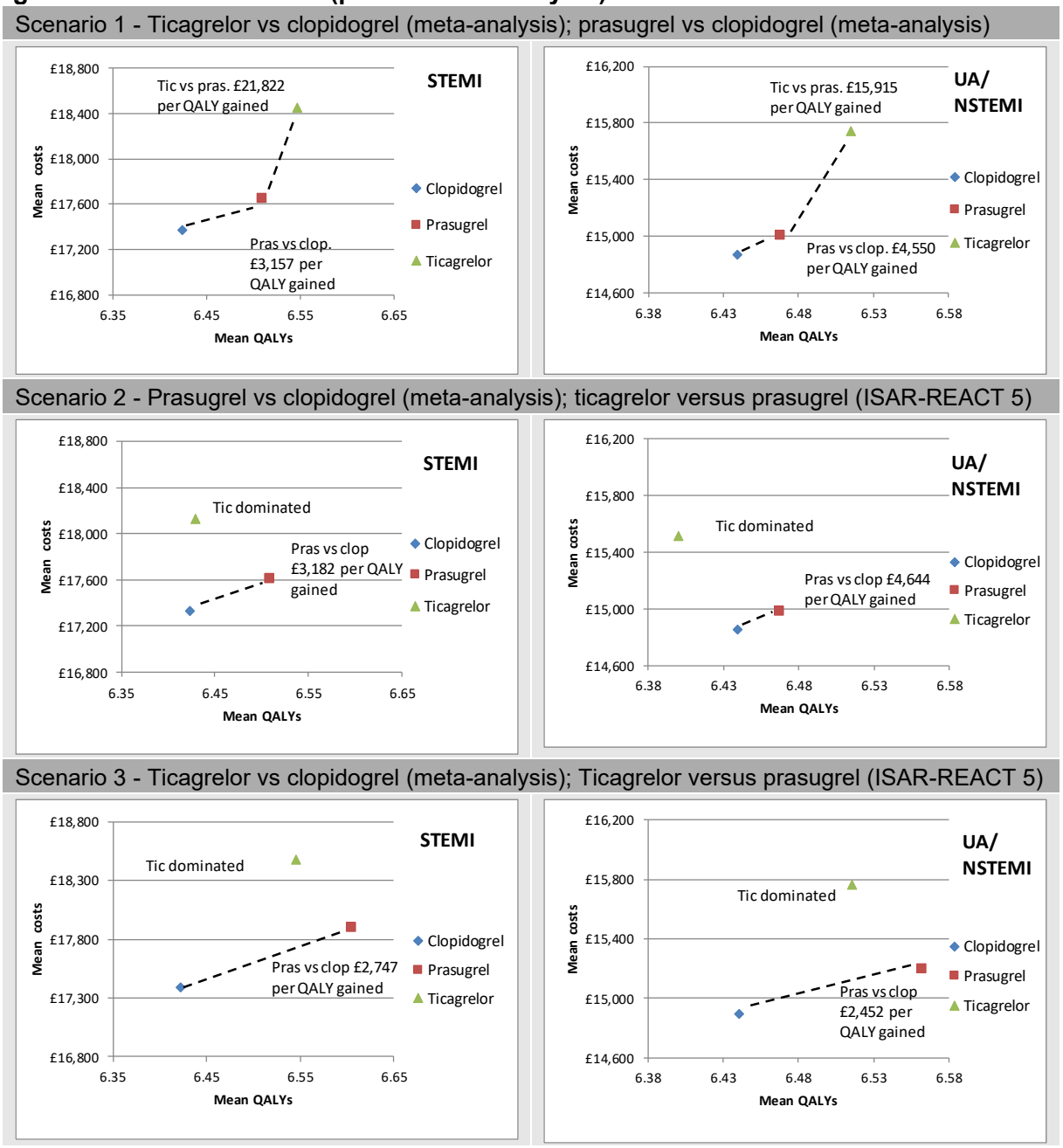
Table 49: Base case analysis results (probabilistic analysis) – cost effectiveness results (mean per person)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k*	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k**
Scenario 1 – Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)														
STEMI														
Clopidogrel	£23,123	£17,369	13.05	8.29	6.42				£111,108	3	0%	6%	94%	0%
Prasugrel	£23,473	£17,639	13.22	8.40	6.51	£270	0.09	£3,157	£112,546	1	53%	43%	4%	42%
Ticagrelor	£24,374	£18,448	13.31	8.45	6.55	£809	0.04	£21,822	£112,479	2	47%	51%	2%	58%
UA/NSTEMI														
Clopidogrel	£19,358	£14,869	12.95	8.21	6.44				£113,922	3	0%	17%	83%	0%
Prasugrel	£19,509	£15,002	13.01	8.25	6.47	£133	0.03	£4,550	£114,373	2	37%	48%	16%	21%
Ticagrelor	£20,303	£15,739	13.11	8.31	6.52	£737	0.05	£15,915	£114,562	1	63%	36%	1%	79%
Scenario 2 – Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	£23,073	£17,334	13.05	8.29	6.42				£111,139	2	4%	69%	28%	3%
Prasugrel	£23,424	£17,605	13.23	8.40	6.51	£270	0.08	£3,182	£112,568	1	91%	7%	2%	90%
Ticagrelor	£23,900	£18,131	13.07	8.30	6.43	£526	-0.08	Dominated	£110,452	3	5%	24%	71%	7%
UA/NSTEMI														
Clopidogrel	£19,334	£14,854	12.95	8.21	6.44				£113,925	2	16%	80%	4%	14%
Prasugrel	£19,484	£14,987	13.01	8.25	6.47	£133	0.03	£4,644	£114,364	1	82%	16%	2%	82%
Ticagrelor	£19,981	£15,522	12.87	8.16	6.40	£535	-0.07	Dominated	£112,472	3	2%	4%	94%	4%
Scenario 3 – Ticagrelor vs clopidogrel (meta-analysis); Ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	£23,149	£17,390	13.05	8.29	6.42				£111,065	3	0%	2%	98%	0%
Prasugrel	£23,842	£17,891	13.42	8.53	6.61	£501	0.18	£2,747	£114,213	1	95%	5%	0%	93%
Ticagrelor	£24,402	£18,471	13.31	8.45	6.55	£580	-0.06	Dominated	£112,442	2	5%	93%	2%	7%
UA/NSTEMI														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k*	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k**
Clopidogrel	£19,396	£14,898	12.95	8.21	6.44				£113,902	3	0%	2%	99%	0%
Prasugrel	£19,791	£15,199	13.21	8.37	6.56	£301	0.12	£2,452	£116,054	1	99%	1%	0%	98%
Ticagrelor	£20,342	£15,768	13.11	8.31	6.52	£569	-0.05	Dominated	£114,539	2	1%	98%	1%	2%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years; undisc = undiscounted
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Figure 6: Base case results (probabilistic analysis)



Abbreviations: QALYs: quality-adjusted life years

Figure 7: Base case results (probabilistic analysis) for scenario 1 – ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis) scatter plots

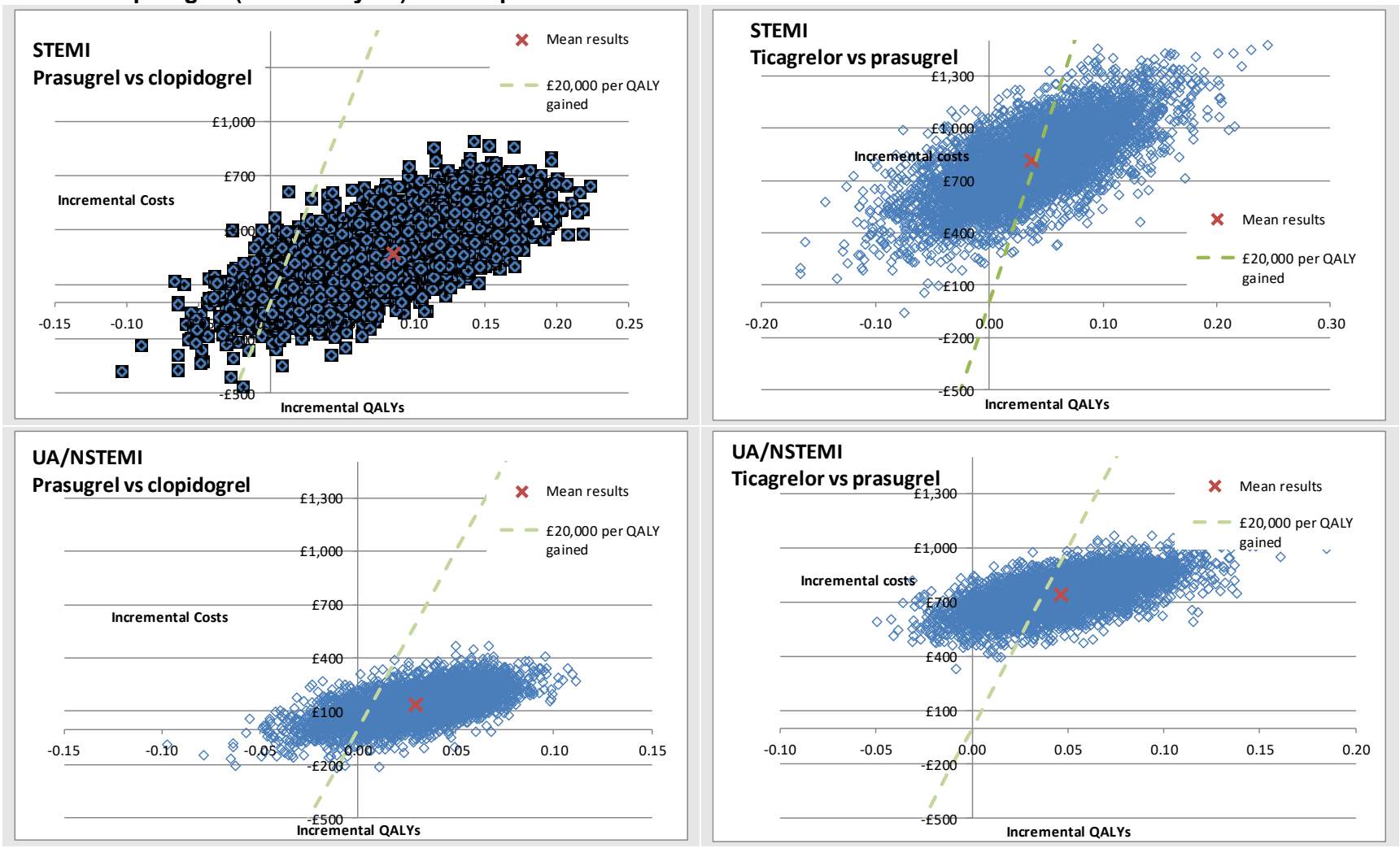


Figure 8: Base case results (probabilistic analysis) for scenario 2 – prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5) scatter plots

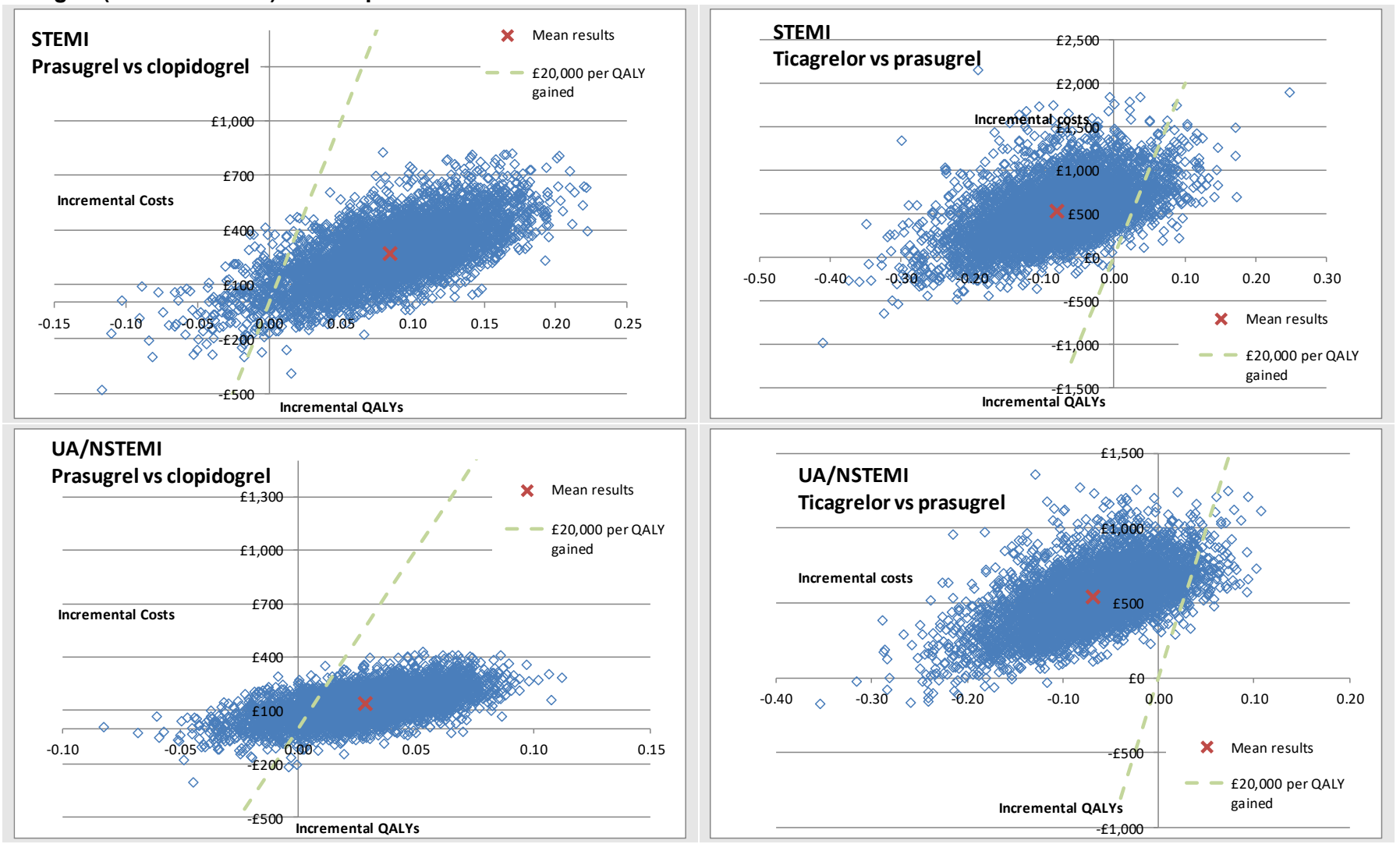


Figure 9: Base case results (probabilistic analysis) for scenario 3 – ticagrelor vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5) scatter plots

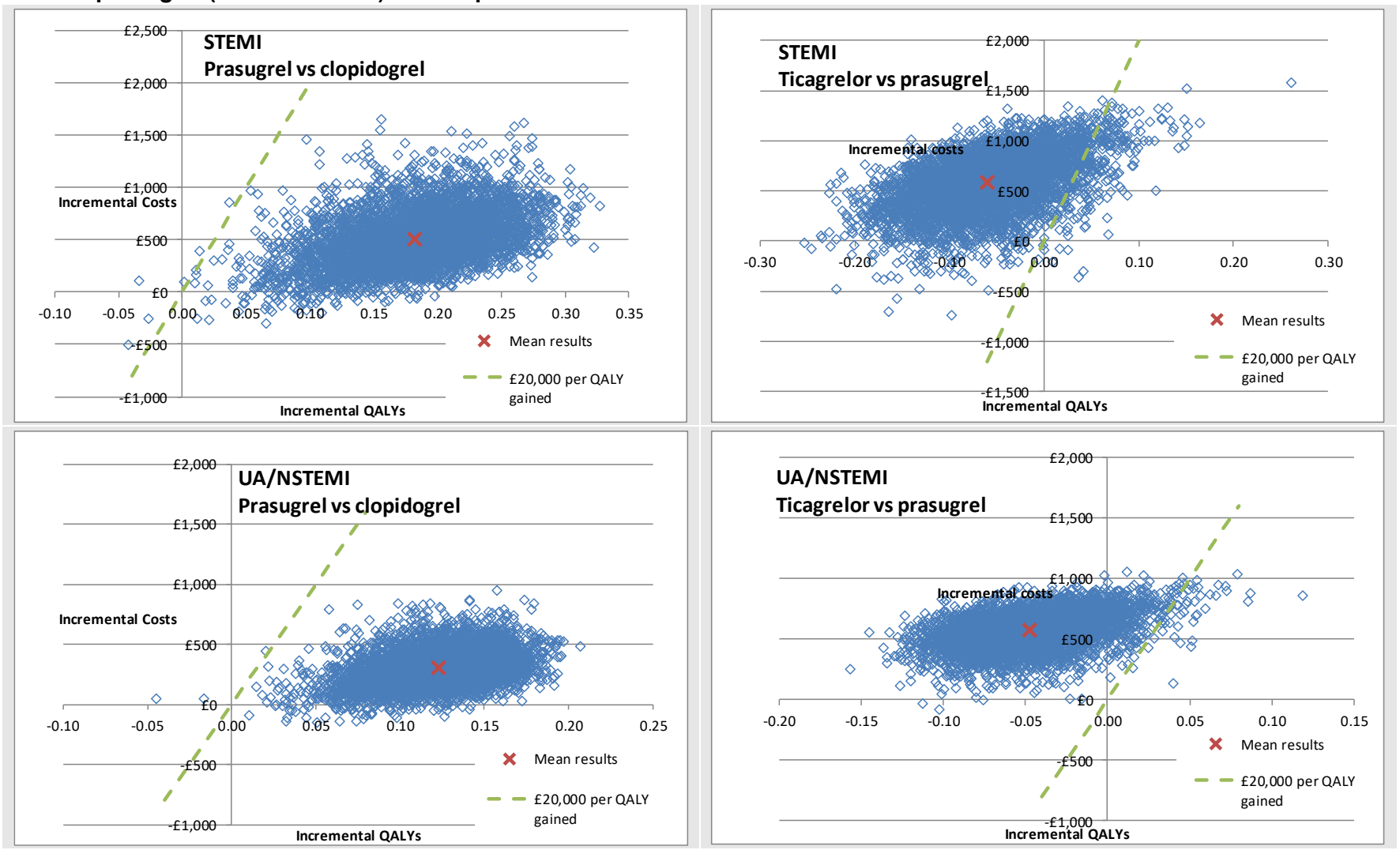


Table 50: Base case analysis results (probabilistic analysis) – events per 1000

Intervention	Reinfarction				Stroke				Major bleed			Minor bleed		
	0 – 30 days	31 days – 1 year	Post 1 year	Total	0 – 30 days	31 days – 1 year	Post 1 year	Total	0 – 30 days	31 days – 1 year	Total	0 – 30 days	31 days – 1 year	Total
Scenario 1 – Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)														
STEMI														
Clopidogrel	29.2	36.5	341.8	407.4	3.0	9.5	89.7	102.2	9.4	25.3	34.6	7.1	19.0	26.1
Prasugrel	23.6	28.0	352.1	403.7	2.5	9.0	92.4	103.9	9.3	36.0	45.3	5.3	38.0	43.2
Ticagrelor	20.1	30.4	353.6	404.1	3.8	10.8	92.8	107.4	9.4	26.5	35.9	9.1	26.0	35.1
UA/NSTEMI														
Clopidogrel	10.3	32.1	326.1	368.4	1.1	5.2	52.8	59.1	6.4	17.3	23.8	4.1	11.0	15.1
Prasugrel	8.2	24.4	330.9	363.5	0.9	4.8	53.6	59.4	6.4	24.6	31.0	3.0	22.0	25.1
Ticagrelor	7.0	26.6	332.7	366.3	1.4	5.9	53.6	60.9	6.4	18.1	24.5	5.2	15.0	20.3
Scenario 2 – Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	29.2	36.3	341.1	406.6	3.0	9.5	89.8	102.2	9.4	25.3	34.7	7.1	19.0	26.1
Prasugrel	23.6	27.9	351.3	402.8	2.5	8.9	92.5	103.9	9.3	36.2	45.5	5.3	38.9	44.2
Ticagrelor	20.2	44.4	340.8	405.4	3.8	10.3	89.7	103.8	9.4	38.4	47.7	9.1	26.1	35.2
UA/NSTEMI														
Clopidogrel	10.2	32.1	325.9	368.2	1.1	5.2	52.9	59.1	6.5	17.4	23.8	4.1	11.0	15.1
Prasugrel	8.2	24.4	330.7	363.3	0.9	4.8	53.6	59.4	6.4	24.7	31.1	3.0	22.7	25.7
Ticagrelor	7.0	39.0	322.2	368.2	1.4	5.6	53.6	60.6	6.4	26.3	32.7	5.2	15.1	20.3
Scenario 3 – Ticagrelor vs clopidogrel (meta-analysis); Ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	29.1	36.5	342.1	407.8	3.0	9.5	89.6	102.0	9.4	25.3	34.7	7.1	19.1	26.2
Prasugrel	23.5	18.9	361.5	403.9	2.5	9.3	94.6	106.4	9.3	25.1	34.4	5.3	38.8	44.0
Ticagrelor	20.1	30.4	354.0	404.5	3.8	10.8	92.7	107.3	9.4	26.5	35.9	9.1	26.2	35.3
UA/NSTEMI														

Intervention	Reinfarction				Stroke				Major bleed			Minor bleed		
Clopidogrel	10.2	32.0	325.4	367.6	1.1	5.2	52.9	59.1	6.4	17.4	23.8	4.1	11.0	15.1
Prasugrel	8.2	16.4	337.9	362.5	0.9	5.0	54.9	60.8	6.4	17.1	23.5	3.1	22.5	25.6
Ticagrelor	7.0	26.5	332.0	365.5	1.4	5.9	54.9	62.1	6.4	18.1	24.5	5.3	15.1	20.3

Table 51: Base case analysis results (probabilistic analysis) – cost breakdown (mean per person)

	0 – 1 year						Post 1 year			Total costs	
	Intervention costs	No further event	Reinfarction	Stroke	Major bleed	Minor bleed	No further event	Reinfarction	Stroke	Undiscounted	Discounted
Scenario 1 – Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)											
STEMI											
Clopidogrel	£26	£1,447	307	£184	£68	£5	£7,116	£6,352	£7,618	£23,123	£17,369
Prasugrel	£151	£1,479	242	£168	£89	£8	£7,330	£6,283	£7,725	£23,473	£17,639
Ticagrelor	£677	£1,480	235	£217	£70	£6	£7,360	£6,293	£8,034	£24,374	£18,448
UA/NSTEMI											
Clopidogrel	£27	£1,555	193	£91	£46	£3	£8,068	£5,323	£4,052	£19,358	£14,869
Prasugrel	£155	£1,568	149	£83	£61	£4	£8,186	£5,241	£4,062	£19,509	£15,002
Ticagrelor	£703	£1,570	152	£106	£48	£4	£8,231	£5,284	£4,206	£20,303	£15,739
Scenario 2 – Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)											
STEMI											
Clopidogrel	£26	£1,448	£307	£184	£68	£5	£7,147	£6,262	£7,626	£23,073	£17,334
Prasugrel	£151	£1,480	£241	£168	£89	£8	£7,361	£6,193	£7,733	£23,424	£17,605
Ticagrelor	£672	£1,468	£296	£209	£93	£6	£7,143	£6,247	£7,764	£23,900	£18,131
UA/NSTEMI											
Clopidogrel	£27	£1,557	£193	£91	£47	£3	£8,094	£5,267	£4,055	£19,334	£14,854
Prasugrel	£155	£1,569	£149	£83	£61	£5	£8,212	£5,186	£4,065	£19,484	£14,987
Ticagrelor	£698	£1,558	£207	£102	£64	£4	£8,002	£5,273	£4,073	£19,981	£15,522
Scenario 3 – Ticagrelor vs clopidogrel (meta-analysis); Ticagrelor versus prasugrel (ISAR-REACT 5)											
STEMI											
Clopidogrel	£26	£1,450	£308	£184	£68	£5	£7,136	£6,365	£7,608	£23,149	£17,390
Prasugrel	£152	£1,492	£203	£174	£67	£8	£7,537	£6,288	£7,922	£23,842	£17,891

	0 – 1 year						Post 1 year			Total costs	
Ticagrelor	£677	£1,483	£236	£217	£70	£6	£7,381	£6,306	£8,025	£24,402	£18,471
UA/NSTEMI											
Clopidogrel	£27	£1,558	£192	£91	£47	£3	£8,104	£5,322	£4,052	£19,396	£14,898
Prasugrel	£156	£1,581	£114	£86	£46	£5	£8,413	£5,227	£4,164	£19,791	£15,199
Ticagrelor	£703	£1,573	£152	£106	£48	£4	£8,267	£5,283	£4,206	£20,342	£15,768

3.2 Sensitivity analyses

In addition to probabilistic sensitivity analysis a range of one-way and scenario sensitivity analyses were undertaken (described in section 2.4) including varying the baseline risk of stroke, inclusion of stroke treatment effects, inclusion of dyspnoea as a side effect, varying bleeding and stroke costs, varying dosing assumptions, incorporation of post-ACS rivaroxaban use, varying event-related mortality in the extrapolation model and varying the baseline risk of stroke and reinfarction to account for overestimation of people alive with an event. Results from the sensitivity analyses are presented for scenario 1 in **Error! Reference source not found.** (STEMI) and **Error! Reference source not found.** (UA/NSTEMI), for scenario 2 in Table 54 (STEMI) and Table 55 (UA/NSTEMI) and for scenario 3 in Table 56 (STEMI) and Table 57 (UA/NSTEMI).

Conclusions about which DAPT option was the most cost effective were unchanged in most sensitivity analyses. However, in scenario 1 for the STEMI population, some sensitivity analyses impacted conclusions. Firstly, when the stroke treatment effects for prasugrel and ticagrelor were not included, ticagrelor became the most cost effective option. When both intervention's treatment effects were not applied, ticagrelor was the most cost effective option with an ICER of £14,946 per QALY gained. This was because ticagrelor had slightly more strokes and prasugrel had slightly less compared to clopidogrel in the base case, whereas this sensitivity analysis resulted in all three strategies having the same number of strokes, which resulted in smaller incremental costs and slightly more incremental QALYs between ticagrelor and prasugrel. When ticagrelor's stroke treatment effect wasn't included but prasugrel's was, ticagrelor was the most cost effective option with an ICER of £17,418 per QALY gained. This was slightly higher than the previous analysis as although ticagrelor was not associated with more strokes than clopidogrel, prasugrel had slightly less strokes, resulting in an increase in incremental costs and very small decrease in incremental QALYs. When prasugrel's stroke treatment effect was not included and ticagrelor's was included, ticagrelor was the most cost effective option with an ICER of £19,268 per QALY gained. The ICER increased slightly because ticagrelor resulted in more strokes compared to prasugrel and clopidogrel, and therefore higher incremental costs and slightly less incremental QALYs. Overall, these analyses made ticagrelor the most cost effective option but the degree of uncertainty was very high, with ticagrelor being the most cost effective option in 51% to 58% of simulations.

Another sensitivity analysis that impacted conclusions in data scenario 1 for STEMI, was when the stroke baseline risks at 1 year were adjusted based on the PLATO trial instead of the Swedeheart data and ticagrelor became the most cost effective option. This was because there were less strokes when the PLATO data was used to inform baseline risks, and as a result smaller incremental costs between ticagrelor and prasugrel. However ticagrelor was only the most cost effective option in 51% of simulations. When the utilities were not age-adjusted ticagrelor became the most cost effective option, with an ICER of £17,350 per QALY gained. This was because the incremental QALYs between ticagrelor and prasugrel were slightly higher. However, ticagrelor was only the most cost effective option in 53% of simulations. Lastly, when the discount rate of 1.5% was used ticagrelor's ICER was just below the threshold at £19,762 per QALY gained. Prasugrel remained the most cost effective option in the rest of the analyses. The different conclusions from these sensitivity analyses highlights that there is a high level of uncertainty between prasugrel and ticagrelor for STEMI in this scenario.

In the sensitivity analyses where rivaroxaban was incorporated into the clopidogrel group conclusions about which option was the most cost effective were not changed however relative costs and QALYs between comparators did vary. In all data scenarios the clopidogrel group now had the highest costs (due to the increase intervention costs of also having rivaroxaban). QALYs were also increased due to the additional treatment effects of

rivaroxaban. In scenario 1, QALYs with clopidogrel (incorporating rivaorixaban) were lower than with ticagrelor and so the clopidogrel option was still not cost effective as it was dominated (higher costs and lower QALYs than an alternative) for both STEMI and UA/NSTEMI. In scenario 2, clopidogrel had both the highest costs and QALYs but was not cost effective as the incremental cost effectiveness ratio was £33,684 per QALY gained for STEMI and £24,348 per QALY gained for UA/NSTEMI. Uncertainty was however increased in this analysis and prasugrel was the most cost effective option in 58% of simulations rather than 82% as in the base case for UA/NSTEMI and 61% of simulations instead of 91% of simulations for STEMI. For scenario 3 QALYs with clopidogrel were lower than prasugrel for both STEMI and UA/NSTEMI and so the clopidogrel option was still not cost effective as it was dominated (higher costs and lower QALYs than an alternative).

Table 52: Sensitivity analyses results for scenario 1: STEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£23,123	£17,369	13.05	8.29	6.42				£111,108	3	0%	6%	94%	0%
Prasugrel	£23,473	£17,639	13.22	8.40	6.51	£270	0.09	£3,157	£112,546	1	53%	43%	4%	42%
Ticagrelor	£24,374	£18,448	13.31	8.45	6.55	£809	0.04	£21,822	£112,479	2	47%	51%	2%	58%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£19,681	£14,967	13.08	8.36	6.47				£114,436	3	0%	5%	95%	0%
Prasugrel	£19,972	£15,199	13.26	8.47	6.56	£233	0.09	£2,662	£115,951	2	50%	46%	4%	40%
Ticagrelor	£20,772	£15,930	13.34	8.52	6.60	£731	0.04	£19,140	£115,984	1	50%	48%	1%	60%
SA2: Rivaroxaban treatment effect included														
Prasugrel	£23,428	£17,604	13.23	8.40	6.51				£112,602	1	43%	31%	27%	31%
Ticagrelor	£24,327	£18,412	13.31	8.45	6.55	£808	0.04	£21,354	£112,551	2	35%	40%	25%	41%
Clopidogrel	£24,390	£18,505	13.29	8.44	6.54	£93	-0.01	Dominated	£112,243	3	23%	29%	48%	28%
SA3: Utilities not age-adjusted														
Clopidogrel	£23,061	£17,328	13.05	10.76	8.27				£148,067	3	0%	5%	95%	0%
Prasugrel	£23,419	£17,603	13.23	10.91	8.38	£275	0.11	£2,448	£150,041	2	47%	49%	4%	39%
Ticagrelor	£24,311	£18,406	13.31	10.97	8.43	£804	0.05	£17,350	£150,164	1	53%	46%	1%	61%
SA4: Dyspnoea included in analysis														
Clopidogrel	£23,086	£17,347	13.05	8.29	6.42				£111,114	3	0%	5%	95%	0%
Prasugrel	£23,443	£17,622	13.23	8.40	6.51	£275	0.09	£3,172	£112,572	1	52%	44%	4%	42%
Ticagrelor	£24,346	£18,434	13.31	8.45	6.55	£812	0.04	£21,561	£112,513	2	47%	51%	1%	58%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£23,093	£17,352	13.05	8.29	6.42				£111,096	3	0%	6%	94%	0%
Prasugrel	£23,461	£17,638	13.23	8.40	6.51	£286	0.09	£3,295	£112,546	1	53%	43%	4%	43%
Ticagrelor	£24,350	£18,437	13.31	8.45	6.55	£799	0.04	£21,957	£112,475	2	47%	52%	2%	57%
SA6: Major bleeding costs including intracranial bleeds (10%)														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Clopidogrel	£23,027	£17,304	13.05	8.29	6.42				£111,187	3	0%	6%	94%	0%
Prasugrel	£23,384	£17,579	13.23	8.40	6.51	£275	0.09	£3,170	£112,647	1	53%	43%	4%	42%
Ticagrelor	£24,282	£18,387	13.31	8.45	6.55	£808	0.04	£21,987	£112,574	2	47%	51%	2%	58%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£23,061	£17,331	13.05	8.29	6.42				£111,166	3	0%	5%	95%	0%
Prasugrel	£23,417	£17,606	13.23	8.40	6.51	£275	0.09	£3,175	£112,623	1	54%	42%	4%	44%
Ticagrelor	£24,315	£18,413	13.31	8.45	6.55	£807	0.04	£21,999	£112,549	2	46%	52%	2%	56%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£23,095	£17,353	13.05	8.29	6.43				£111,176	3	0%	6%	94%	0%
Prasugrel	£23,457	£17,633	13.23	8.41	6.51	£280	0.09	£3,190	£112,650	1	55%	41%	4%	44%
Ticagrelor	£24,343	£18,430	13.31	8.45	6.55	£797	0.04	£22,606	£112,558	2	45%	53%	2%	56%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£23,156	£17,399	13.05	8.29	6.42				£111,086	3	0%	6%	94%	0%
Prasugrel	£23,519	£17,680	13.23	8.40	6.51	£281	0.09	£3,232	£112,543	1	53%	43%	4%	43%
Ticagrelor	£24,408	£18,479	13.31	8.45	6.55	£799	0.04	£21,913	£112,474	2	47%	52%	2%	57%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£23,128	£17,379	13.05	8.29	6.42				£111,120	3	0%	6%	94%	0%
Prasugrel	£23,496	£17,666	13.23	8.40	6.51	£287	0.09	£3,312	£112,568	1	52%	44%	4%	42%
Ticagrelor	£24,387	£18,467	13.31	8.45	6.55	£800	0.04	£21,200	£112,522	2	48%	51%	2%	58%
SA11: Percentage stroke social care costs publically funded - 30%														
Clopidogrel	£21,324	£16,150	13.05	8.29	6.42				£112,339	3	0%	5%	94%	0%
Prasugrel	£21,658	£16,412	13.23	8.40	6.51	£262	0.09	£3,026	£113,808	1	51%	45%	4%	41%
Ticagrelor	£22,470	£17,155	13.31	8.45	6.55	£743	0.04	£20,130	£113,803	2	49%	50%	2%	59%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£24,831	£18,520	13.05	8.29	6.42				£109,952	3	0%	5%	94%	0%
Prasugrel	£25,205	£18,804	13.23	8.40	6.51	£284	0.09	£3,280	£111,397	1	55%	41%	4%	44%
Ticagrelor	£26,192	£19,678	13.31	8.45	6.55	£874	0.04	£23,137	£111,279	2	45%	54%	2%	56%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
SA13: Clopidogrel 300mg loading dose														
Clopidogrel	£23,169	£17,405	13.05	8.29	6.42				£111,065	3	0%	5%	94%	0%
Prasugrel	£23,524	£17,678	13.23	8.40	6.51	£273	0.09	£3,134	£112,535	1	54%	42%	4%	43%
Ticagrelor	£24,426	£18,488	13.31	8.45	6.55	£810	0.04	£22,311	£112,451	2	46%	53%	1%	57%
SA14: Stroke treatment effect excluded														
Clopidogrel	£23,075	£17,336	13.05	8.29	6.42				£111,118	3	0%	6%	94%	0%
Prasugrel	£23,521	£17,683	13.23	8.40	6.51	£347	0.09	£4,053	£112,483	2	42%	53%	5%	35%
Ticagrelor	£24,165	£18,288	13.31	8.45	6.55	£605	0.04	£14,946	£112,687	1	58%	41%	1%	65%
SA15: Ticagrelor's stroke treatment effect not included														
Clopidogrel	£23,116	£17,365	13.05	8.29	6.42				£111,125	3	0%	5%	95%	0%
Prasugrel	£23,467	£17,636	13.23	8.40	6.51	£271	0.09	£3,153	£112,572	2	47%	49%	4%	39%
Ticagrelor	£24,203	£18,313	13.31	8.45	6.55	£678	0.04	£17,418	£112,673	1	53%	46%	1%	61%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£23,109	£17,356	13.05	8.29	6.42				£111,113	3	0%	7%	93%	0%
Prasugrel	£23,552	£17,699	13.23	8.40	6.51	£343	0.08	£4,037	£112,469	2	49%	46%	5%	39%
Ticagrelor	£24,356	£18,432	13.31	8.45	6.55	£733	0.04	£19,268	£112,497	1	51%	48%	2%	61%
SA18: Reduce SMR for ACS/Reinfarction by 20%														
Clopidogrel	£24,816	£18,353	14.18	8.97	6.83				£118,166	3	0%	6%	94%	0%
Prasugrel	£25,188	£18,635	14.37	9.09	6.92	£282	0.09	£3,086	£119,712	1	53%	43%	4%	43%
Ticagrelor	£26,092	£19,446	14.45	9.14	6.95	£811	0.04	£21,874	£119,643	2	47%	51%	2%	57%
SA19: Include baseline risk adjustment														
Clopidogrel	£21,864	£16,430	13.16	8.38	6.48				£113,196	3	0%	5%	95%	0%
Prasugrel	£22,195	£16,689	13.34	8.50	6.57	£259	0.09	£2,974	£114,680	1	50%	45%	4%	40%
Ticagrelor	£23,061	£17,470	13.43	8.55	6.61	£781	0.04	£20,168	£114,673	2	50%	49%	1%	60%
SA20: Discount rate 1.5%														
Clopidogrel	£23,135	£20,322	13.05	8.29	7.39				£127,384	3	0%	5%	95%	0%
Prasugrel	£23,488	£20,635	13.22	8.40	7.49	£313	0.10	£3,127	£129,072	2	50%	46%	4%	40%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Ticagrelor	£24,385	£21,488	13.31	8.45	7.53	£853	0.04	£19,762	£129,082	1	49%	49%	1%	60%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Table 53: Sensitivity analyses results for scenario 1: UA/NSTEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£19,358	£14,869	12.95	8.21	6.44				£113,922	3	0%	17%	83%	0%
Prasugrel	£19,509	£15,002	13.01	8.25	6.47	£133	0.03	£4,550	£114,373	2	37%	48%	16%	21%
Ticagrelor	£20,303	£15,739	13.11	8.31	6.52	£737	0.05	£15,915	£114,562	1	63%	36%	1%	79%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£16,951	£13,172	12.98	8.26	6.47				£116,302	3	0%	15%	85%	0%
Prasugrel	£17,094	£13,302	13.04	8.30	6.50	£130	0.03	£4,312	£116,774	2	32%	54%	14%	18%
Ticagrelor	£17,817	£13,984	13.14	8.36	6.55	£681	0.05	£14,507	£117,032	1	68%	32%	0%	82%
SA2: Rivaroxaban treatment effect included														
Prasugrel	£19,481	£14,980	13.01	8.25	6.47				£114,415	2	31%	34%	35%	16%
Ticagrelor	£20,273	£15,715	13.11	8.31	6.52	£735	0.05	£15,867	£114,607	1	51%	36%	13%	61%
Clopidogrel	£20,312	£15,770	13.08	8.29	6.50	£54	-0.01	Dominated	£114,262	3	18%	30%	52%	22%
SA3: Utilities not age-adjusted														
Clopidogrel	£19,327	£14,849	12.95	10.76	8.37				£152,602	3	0%	14%	86%	0%
Prasugrel	£19,482	£14,985	13.02	10.81	8.41	£136	0.04	£3,447	£153,254	2	26%	61%	14%	16%
Ticagrelor	£20,273	£15,720	13.11	10.89	8.47	£735	0.06	£12,316	£153,713	1	74%	25%	0%	84%
SA4: Dyspnoea included in analysis														
Clopidogrel	£19,341	£14,860	12.96	8.21	6.44				£113,939	3	0%	16%	84%	0%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Prasugrel	£19,495	£14,996	13.02	8.25	6.47	£135	0.03	£4,556	£114,397	2	36%	48%	15%	21%
Ticagrelor	£20,291	£15,735	13.11	8.31	6.52	£739	0.05	£15,929	£114,586	1	63%	36%	1%	79%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£19,344	£14,863	12.95	8.21	6.44				£113,901	3	0%	17%	83%	0%
Prasugrel	£19,505	£15,004	13.01	8.25	6.47	£142	0.03	£4,742	£114,357	2	37%	47%	16%	21%
Ticagrelor	£20,293	£15,736	13.11	8.31	6.51	£732	0.05	£15,956	£114,542	1	63%	36%	1%	79%
SA6: Major bleeding costs including intracranial bleeds (10%)														
Clopidogrel	£19,296	£14,828	12.96	8.21	6.44				£113,994	3	0%	16%	84%	0%
Prasugrel	£19,452	£14,964	13.02	8.25	6.47	£137	0.03	£4,549	£114,458	2	37%	48%	15%	21%
Ticagrelor	£20,243	£15,699	13.11	8.31	6.52	£735	0.05	£16,107	£114,636	1	63%	37%	1%	79%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£19,330	£14,855	12.95	8.21	6.44				£113,951	3	0%	16%	84%	0%
Prasugrel	£19,484	£14,990	13.01	8.25	6.47	£136	0.03	£4,559	£114,411	2	37%	49%	15%	21%
Ticagrelor	£20,277	£15,725	13.11	8.31	6.52	£735	0.05	£16,040	£114,592	1	63%	36%	1%	79%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£19,346	£14,864	12.95	8.21	6.44				£113,970	3	0%	16%	84%	0%
Prasugrel	£19,504	£15,002	13.02	8.25	6.47	£138	0.03	£4,564	£114,438	2	37%	48%	14%	22%
Ticagrelor	£20,290	£15,732	13.11	8.31	6.52	£730	0.05	£16,145	£114,612	1	62%	36%	1%	78%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£19,407	£14,911	12.95	8.21	6.44				£113,878	3	0%	16%	84%	0%
Prasugrel	£19,564	£15,049	13.01	8.25	6.47	£138	0.03	£4,659	£114,334	2	36%	49%	15%	21%
Ticagrelor	£20,353	£15,781	13.11	8.31	6.52	£732	0.05	£15,868	£114,524	1	64%	35%	1%	79%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£19,366	£14,879	12.95	8.21	6.44				£113,942	3	0%	16%	84%	0%
Prasugrel	£19,527	£15,022	13.01	8.25	6.47	£143	0.03	£4,796	£114,395	2	35%	50%	15%	20%
Ticagrelor	£20,315	£15,753	13.11	8.31	6.52	£731	0.05	£15,767	£114,591	1	65%	34%	1%	80%
SA11: Percentage stroke social care costs publically funded - 30%														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Clopidogrel	£18,413	£14,220	12.95	8.21	6.44				£114,590	3	0%	17%	82%	0%
Prasugrel	£18,564	£14,354	13.01	8.25	6.47	£134	0.03	£4,580	£115,041	2	34%	50%	16%	20%
Ticagrelor	£19,318	£15,061	13.11	8.31	6.52	£707	0.05	£15,208	£115,263	1	66%	33%	1%	80%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£20,226	£15,460	12.95	8.21	6.44				£113,335	3	0%	16%	84%	0%
Prasugrel	£20,378	£15,593	13.01	8.25	6.47	£133	0.03	£4,522	£113,789	2	38%	47%	15%	21%
Ticagrelor	£21,212	£16,360	13.11	8.31	6.52	£767	0.05	£16,367	£113,960	1	62%	37%	1%	79%
SA13: Clopidogrel 300mg loading dose														
Clopidogrel	£19,411	£14,911	12.96	8.21	6.44				£113,883	3	0%	16%	84%	0%
Prasugrel	£19,562	£15,044	13.02	8.25	6.47	£133	0.03	£4,483	£114,345	2	37%	48%	15%	21%
Ticagrelor	£20,359	£15,783	13.11	8.31	6.52	£739	0.05	£16,016	£114,529	1	63%	36%	1%	79%
SA14: Stroke treatment effect excluded														
Clopidogrel	£19,330	£14,851	12.95	8.21	6.44				£113,925	3	0%	17%	83%	0%
Prasugrel	£19,524	£15,018	13.01	8.25	6.47	£168	0.03	£5,826	£114,333	2	27%	56%	17%	16%
Ticagrelor	£20,200	£15,660	13.11	8.31	6.52	£642	0.05	£13,311	£114,655	1	73%	27%	0%	84%
SA15: Ticagrelor's stroke treatment effect not included														
Clopidogrel	£19,363	£14,874	12.95	8.21	6.44				£113,923	3	0%	16%	84%	0%
Prasugrel	£19,514	£15,008	13.01	8.25	6.47	£133	0.03	£4,536	£114,378	2	31%	53%	16%	18%
Ticagrelor	£20,232	£15,683	13.11	8.31	6.52	£676	0.05	£14,322	£114,646	1	68%	31%	0%	82%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£19,346	£14,857	12.95	8.21	6.44				£113,930	3	0%	18%	82%	0%
Prasugrel	£19,539	£15,024	13.01	8.25	6.47	£167	0.03	£5,761	£114,342	2	33%	50%	17%	20%
Ticagrelor	£20,288	£15,725	13.11	8.31	6.51	£701	0.05	£15,049	£114,573	1	67%	32%	1%	80%
SA17: UA/NSTEMI prasugrel arm receiving clopiodgrel loading dose														
Clopidogrel	£19,353	£14,865	12.95	8.21	6.44				£113,946	3	0%	17%	83%	0%
Prasugrel	£19,504	£14,998	13.01	8.25	6.47	£133	0.03	£4,553	£114,397	2	36%	49%	16%	20%
Ticagrelor	£20,297	£15,735	13.11	8.31	6.52	£736	0.05	£15,866	£114,589	1	64%	34%	2%	80%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
SA18: Reduce SMR for ACS/Reinfarction by 20%														
Clopidogrel	£20,993	£15,843	14.14	8.92	6.87				£121,572	3	0%	16%	84%	0%
Prasugrel	£21,148	£15,978	14.21	8.97	6.90	£134	0.03	£4,324	£122,060	2	35%	50%	16%	21%
Ticagrelor	£21,953	£16,721	14.31	9.03	6.95	£744	0.05	£15,276	£122,290	1	65%	34%	1%	80%
SA19: Include baseline risk adjustment														
Clopidogrel	£18,684	£14,393	12.96	8.23	6.45				£114,620	3	0%	16%	84%	0%
Prasugrel	£18,834	£14,526	13.02	8.27	6.48	£133	0.03	£4,484	£115,080	2	34%	50%	15%	19%
Ticagrelor	£19,608	£15,247	13.12	8.33	6.53	£722	0.05	£15,401	£115,295	1	65%	34%	1%	81%
SA20: Discount rate 1.5%														
Clopidogrel	£19,377	£17,196	12.95	8.21	7.36				£129,970	3	0%	15%	85%	0%
Prasugrel	£19,529	£17,339	13.01	8.25	7.39	£143	0.03	£4,148	£130,515	2	31%	55%	14%	19%
Ticagrelor	£20,322	£18,104	13.11	8.31	7.45	£765	0.05	£14,422	£130,811	1	69%	30%	0%	81%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Table 54: Sensitivity analyses results for scenario 2: STEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£23,073	£17,334	13.05	8.29	6.42				£111,139	2	4%	69%	28%	3%
Prasugrel	£23,424	£17,605	13.23	8.40	6.51	£270	0.08	£3,182	£112,568	1	91%	7%	2%	90%
Ticagrelor	£23,900	£18,131	13.07	8.30	6.43	£526	-0.08	Dominated	£110,452	3	5%	24%	71%	7%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£19,716	£14,991	13.08	8.35	6.47				£114,354	2	3%	69%	29%	2%
Prasugrel	£20,006	£15,223	13.25	8.47	6.55	£232	0.09	£2,661	£115,863	1	92%	6%	2%	90%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Ticagrelor	£20,513	£15,763	13.09	8.36	6.47	£541	-0.08	Dominated	£113,710	3	5%	25%	70%	8%
SA2: Rivaroxaban treatment effect included														
Prasugrel	£23,405	£17,593	13.23	8.41	6.51				£112,660	1	61%	35%	4%	51%
Ticagrelor	£23,885	£18,122	13.06	8.30	6.43	£529	-0.08	Dominated	£110,502	3	3%	9%	88%	3%
Clopidogrel	£24,365	£18,492	13.29	8.44	6.54	£370	0.11	£33,684	£112,295	2	36%	56%	8%	46%
SA3: Utilities not age-adjusted														
Clopidogrel	£23,135	£17,378	13.05	10.76	8.27				£148,046	2	3%	63%	34%	2%
Prasugrel	£23,484	£17,648	13.22	10.91	8.38	£270	0.11	£2,450	£149,977	1	90%	8%	2%	88%
Ticagrelor	£23,952	£18,168	13.06	10.77	8.28	£520	-0.10	Dominated	£147,373	3	7%	28%	64%	9%
SA4: Dyspnoea included in analysis														
Clopidogrel	£23,084	£17,344	13.05	8.29	6.43				£111,158	2	3%	70%	26%	3%
Prasugrel	£23,434	£17,614	13.23	8.40	6.51	£270	0.09	£3,149	£112,601	1	92%	7%	1%	90%
Ticagrelor	£23,913	£18,142	13.06	8.30	6.43	£529	-0.08	Dominated	£110,448	3	5%	23%	72%	7%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£23,108	£17,366	13.05	8.29	6.43				£111,136	2	3%	69%	28%	3%
Prasugrel	£23,478	£17,654	13.23	8.40	6.51	£288	0.09	£3,323	£112,579	1	91%	7%	2%	90%
Ticagrelor	£23,946	£18,172	13.07	8.30	6.43	£519	-0.08	Dominated	£110,452	3	5%	24%	71%	8%
SA6: Major bleeding costs including intracranial bleeds (10%)														
Clopidogrel	£23,115	£17,368	13.05	8.29	6.42				£111,116	2	3%	70%	27%	3%
Prasugrel	£23,469	£17,640	13.23	8.40	6.51	£273	0.09	£3,153	£112,574	1	92%	6%	2%	91%
Ticagrelor	£23,940	£18,163	13.06	8.29	6.43	£522	-0.08	Dominated	£110,409	3	5%	24%	71%	7%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£23,095	£17,355	13.05	8.29	6.43				£111,148	2	3%	70%	27%	2%
Prasugrel	£23,454	£17,632	13.23	8.40	6.51	£277	0.09	£3,178	£112,612	1	92%	6%	1%	91%
Ticagrelor	£23,923	£18,153	13.06	8.30	6.43	£521	-0.08	Dominated	£110,466	3	5%	24%	71%	7%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£23,073	£17,333	13.05	8.29	6.42				£111,111	2	3%	70%	27%	3%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Prasugrel	£23,425	£17,605	13.23	8.40	6.51	£272	0.09	£3,162	£112,560	1	92%	7%	1%	90%
Ticagrelor	£23,893	£18,126	13.06	8.29	6.43	£521	-0.08	Dominated	£110,406	3	5%	24%	72%	7%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£23,128	£17,378	13.05	8.29	6.43				£111,137	2	3%	70%	27%	3%
Prasugrel	£23,482	£17,652	13.22	8.40	6.51	£274	0.09	£3,214	£112,567	1	92%	7%	2%	90%
Ticagrelor	£23,955	£18,176	13.06	8.30	6.43	£524	-0.08	Dominated	£110,425	3	5%	24%	71%	7%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£23,090	£17,356	13.05	8.29	6.42				£111,139	2	3%	70%	27%	2%
Prasugrel	£23,460	£17,645	13.23	8.40	6.51	£289	0.09	£3,327	£112,586	1	92%	6%	2%	90%
Ticagrelor	£23,924	£18,160	13.06	8.30	6.43	£515	-0.08	Dominated	£110,454	3	5%	24%	71%	7%
SA11: Percentage stroke social care costs publically funded - 30%														
Clopidogrel	£21,342	£16,164	13.05	8.29	6.42				£112,292	2	4%	68%	28%	3%
Prasugrel	£21,672	£16,423	13.22	8.40	6.51	£259	0.08	£3,061	£113,726	1	92%	6%	2%	90%
Ticagrelor	£22,127	£16,928	13.06	8.29	6.43	£505	-0.08	Dominated	£111,634	3	5%	26%	70%	7%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£24,909	£18,578	13.05	8.29	6.42				£109,910	2	3%	70%	27%	3%
Prasugrel	£25,283	£18,861	13.23	8.40	6.51	£283	0.09	£3,246	£111,372	1	92%	6%	1%	91%
Ticagrelor	£25,772	£19,402	13.06	8.29	6.43	£541	-0.08	Dominated	£109,177	3	4%	24%	72%	7%
SA13: Clopidogrel 300mg loading dose														
Clopidogrel	£23,133	£17,378	13.05	8.29	6.42				£111,092	2	4%	69%	27%	3%
Prasugrel	£23,487	£17,650	13.23	8.40	6.51	£273	0.09	£3,153	£112,549	1	92%	7%	2%	90%
Ticagrelor	£23,964	£18,177	13.06	8.30	6.43	£527	-0.08	Dominated	£110,411	3	5%	24%	71%	8%
SA14: Stroke treatment effect excluded														
Clopidogrel	£23,101	£17,354	13.05	8.28	6.42				£111,073	2	4%	65%	31%	3%
Prasugrel	£23,545	£17,699	13.22	8.40	6.51	£345	0.08	£4,060	£112,427	1	90%	8%	2%	88%
Ticagrelor	£23,803	£18,052	13.06	8.29	6.43	£353	-0.08	Dominated	£110,509	3	6%	27%	67%	9%
SA15: Ticagrelor's stroke treatment effect not included														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Clopidogrel	£23,035	£17,305	13.05	8.29	6.42				£111,181	2	3%	66%	31%	3%
Prasugrel	£23,390	£17,578	13.23	8.40	6.51	£273	0.09	£3,145	£112,646	1	91%	7%	2%	89%
Ticagrelor	£23,743	£18,006	13.07	8.30	6.43	£428	-0.08	Dominated	£110,643	3	6%	27%	68%	9%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£23,049	£17,320	13.05	8.29	6.42				£111,148	2	4%	69%	28%	3%
Prasugrel	£23,499	£17,669	13.23	8.40	6.51	£349	0.09	£4,048	£112,524	1	91%	7%	1%	90%
Ticagrelor	£23,876	£18,116	13.06	8.30	6.43	£447	-0.08	Dominated	£110,477	3	5%	24%	71%	8%
SA18: Reduce SMR for ACS/Reinfarction by 20%														
Clopidogrel	£24,816	£18,358	14.18	8.97	6.83				£118,153	2	3%	68%	29%	3%
Prasugrel	£25,195	£18,645	14.37	9.09	6.92	£287	0.09	£3,155	£119,687	1	91%	7%	2%	90%
Ticagrelor	£25,640	£19,153	14.19	8.97	6.83	£507	-0.09	Dominated	£117,451	3	6%	25%	70%	8%
SA19: Include baseline risk adjustment														
Clopidogrel	£21,890	£16,449	13.17	8.38	6.48				£113,190	2	3%	68%	29%	3%
Prasugrel	£22,220	£16,707	13.34	8.50	6.57	£258	0.09	£2,958	£114,678	1	92%	7%	1%	90%
Ticagrelor	£22,709	£17,238	13.18	8.39	6.49	£530	-0.08	Dominated	£112,534	3	5%	25%	70%	7%
SA20: Discount rate 1.5%														
Clopidogrel	£23,115	£20,304	13.05	8.29	7.38				£127,367	2	3%	67%	31%	2%
Prasugrel	£23,472	£20,620	13.23	8.40	7.48	£316	0.10	£3,117	£129,079	1	92%	7%	1%	90%
Ticagrelor	£23,945	£21,118	13.06	8.29	7.39	£498	-0.10	Dominated	£126,666	3	6%	26%	68%	8%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Table 55: Sensitivity analyses results for scenario 2: UA/NSTEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£19,334	£14,854	12.95	8.21	6.44				£113,925	2	16%	80%	4%	14%
Prasugrel	£19,484	£14,987	13.01	8.25	6.47	£133	0.03	£4,644	£114,364	1	82%	16%	2%	82%
Ticagrelor	£19,981	£15,522	12.87	8.16	6.40	£535	-0.07	Dominated	£112,472	3	2%	4%	94%	4%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£16,971	£13,186	12.98	8.26	6.47				£116,264	2	14%	81%	5%	12%
Prasugrel	£17,114	£13,315	13.04	8.30	6.50	£129	0.03	£4,305	£116,735	1	84%	14%	2%	84%
Ticagrelor	£17,621	£13,853	12.90	8.21	6.43	£538	-0.07	Dominated	£114,818	3	2%	4%	94%	4%
SA2: Rivaroxaban treatment effect included														
Prasugrel	£19,459	£14,969	13.01	8.25	6.47				£114,446	1	58%	40%	2%	42%
Ticagrelor	£19,961	£15,508	12.88	8.16	6.40	£539	-0.07	Dominated	£112,549	3	1%	4%	94%	2%
Clopidogrel	£20,291	£15,759	13.08	8.29	6.50	£251	0.10	£24,348	£114,305	2	40%	56%	3%	56%
SA3: Utilities not age-adjusted														
Clopidogrel	£19,381	£14,887	12.96	10.76	8.37				£152,605	2	13%	79%	8%	12%
Prasugrel	£19,532	£15,019	13.01	10.81	8.41	£133	0.04	£3,479	£153,236	1	83%	14%	2%	83%
Ticagrelor	£20,026	£15,552	12.88	10.69	8.32	£533	-0.09	Dominated	£150,910	3	3%	7%	90%	5%
SA4: Dyspnoea included in analysis														
Clopidogrel	£19,347	£14,864	12.95	8.21	6.44				£113,951	2	15%	82%	4%	13%
Prasugrel	£19,499	£14,998	13.01	8.25	6.47	£134	0.03	£4,532	£114,407	1	84%	15%	1%	84%
Ticagrelor	£19,998	£15,535	12.87	8.16	6.40	£537	-0.07	Dominated	£112,484	3	2%	3%	95%	3%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£19,359	£14,875	12.95	8.21	6.44				£113,936	2	15%	81%	4%	12%
Prasugrel	£19,521	£15,018	13.01	8.25	6.47	£143	0.03	£4,800	£114,389	1	83%	15%	2%	84%
Ticagrelor	£20,014	£15,550	12.88	8.16	6.40	£532	-0.07	Dominated	£112,494	3	2%	4%	94%	4%
SA6: Major bleeding costs including intracranial bleeds (10%)														
Clopidogrel	£19,368	£14,882	12.96	8.21	6.44				£113,924	2	15%	81%	4%	13%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Prasugrel	£19,521	£15,016	13.01	8.25	6.47	£134	0.03	£4,552	£114,380	1	84%	15%	2%	84%
Ticagrelor	£20,015	£15,550	12.87	8.16	6.40	£534	-0.07	Dominated	£112,461	3	2%	4%	94%	4%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£19,354	£14,871	12.95	8.21	6.44				£113,954	2	15%	81%	5%	13%
Prasugrel	£19,508	£15,007	13.01	8.25	6.47	£136	0.03	£4,589	£114,410	1	83%	15%	2%	84%
Ticagrelor	£20,004	£15,541	12.88	8.16	6.40	£534	-0.07	Dominated	£112,511	3	2%	4%	94%	4%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£19,322	£14,843	12.95	8.21	6.44				£113,932	2	15%	81%	4%	13%
Prasugrel	£19,475	£14,977	13.01	8.25	6.47	£135	0.03	£4,558	£114,389	1	83%	15%	2%	84%
Ticagrelor	£19,969	£15,511	12.87	8.16	6.40	£534	-0.07	Dominated	£112,469	3	2%	4%	94%	4%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£19,370	£14,883	12.95	8.21	6.44				£113,936	2	16%	81%	4%	13%
Prasugrel	£19,525	£15,020	13.01	8.25	6.47	£137	0.03	£4,641	£114,389	1	83%	16%	2%	83%
Ticagrelor	£20,019	£15,553	12.87	8.16	6.40	£533	-0.07	Dominated	£112,469	3	2%	4%	94%	4%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£19,345	£14,868	12.95	8.21	6.44				£113,950	2	15%	81%	5%	13%
Prasugrel	£19,507	£15,011	13.01	8.25	6.47	£143	0.03	£4,841	£114,397	1	83%	15%	2%	83%
Ticagrelor	£19,999	£15,542	12.88	8.16	6.40	£531	-0.07	Dominated	£112,507	3	2%	4%	94%	4%
SA11: Percentage stroke social care costs publically funded - 30%														
Clopidogrel	£18,437	£14,238	12.95	8.21	6.44				£114,545	2	15%	80%	5%	13%
Prasugrel	£18,589	£14,373	13.01	8.25	6.47	£135	0.03	£4,622	£114,993	1	84%	15%	2%	84%
Ticagrelor	£19,077	£14,899	12.87	8.16	6.40	£526	-0.07	Dominated	£113,101	3	2%	5%	94%	3%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£20,302	£15,518	12.95	8.21	6.44				£113,273	2	14%	82%	4%	12%
Prasugrel	£20,453	£15,650	13.01	8.25	6.47	£132	0.03	£4,399	£113,743	1	85%	14%	1%	85%
Ticagrelor	£20,956	£16,192	12.87	8.16	6.40	£542	-0.07	Dominated	£111,797	3	1%	4%	95%	3%
SA13: Clopidogrel 300mg loading dose														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Clopidogrel	£19,383	£14,889	12.95	8.21	6.44				£113,896	2	15%	81%	5%	13%
Prasugrel	£19,535	£15,023	13.01	8.25	6.47	£134	0.03	£4,499	£114,356	1	84%	15%	1%	83%
Ticagrelor	£20,035	£15,560	12.87	8.16	6.40	£537	-0.07	Dominated	£112,449	3	2%	4%	94%	4%
SA14: Stroke treatment effect excluded														
Clopidogrel	£19,338	£14,855	12.95	8.21	6.44				£113,918	2	16%	80%	4%	14%
Prasugrel	£19,533	£15,023	13.01	8.25	6.47	£168	0.03	£5,761	£114,334	1	82%	16%	2%	82%
Ticagrelor	£19,932	£15,479	12.87	8.16	6.40	£456	-0.07	Dominated	£112,521	3	2%	4%	93%	5%
SA15: Ticagrelor's stroke treatment effect not included														
Clopidogrel	£19,285	£14,815	12.95	8.21	6.44				£113,984	2	14%	81%	5%	13%
Prasugrel	£19,438	£14,950	13.01	8.25	6.47	£135	0.03	£4,490	£114,449	1	84%	14%	2%	83%
Ticagrelor	£19,883	£15,443	12.88	8.16	6.40	£494	-0.07	Dominated	£112,619	3	2%	5%	93%	4%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£19,313	£14,839	12.96	8.21	6.44				£113,974	2	17%	79%	4%	14%
Prasugrel	£19,509	£15,008	13.02	8.25	6.47	£169	0.03	£5,790	£114,390	1	82%	17%	2%	82%
Ticagrelor	£19,962	£15,508	12.88	8.16	6.40	£499	-0.07	Dominated	£112,533	3	2%	4%	94%	4%
SA17: UA/NSTEMI prasugrel arm receiving clopiodgrel loading dose														
Clopidogrel	£19,380	£14,887	12.96	8.21	6.44				£113,938	2	15%	81%	5%	13%
Prasugrel	£19,529	£15,019	13.01	8.25	6.47	£132	0.03	£4,462	£114,397	1	84%	15%	2%	84%
Ticagrelor	£20,025	£15,553	12.88	8.16	6.40	£535	-0.07	Dominated	£112,492	3	1%	5%	94%	4%
SA18: Reduce SMR for ACS/Reinfarction by 20%														
Clopidogrel	£21,011	£15,859	14.14	8.92	6.87				£121,566	2	15%	80%	5%	13%
Prasugrel	£21,169	£15,996	14.21	8.97	6.90	£138	0.03	£4,441	£122,048	1	83%	15%	2%	83%
Ticagrelor	£21,647	£16,520	14.05	8.87	6.83	£524	-0.07	Dominated	£120,057	3	2%	4%	93%	4%
SA19: Include baseline risk adjustment														
Clopidogrel	£18,716	£14,418	12.96	8.23	6.45				£114,590	2	14%	82%	4%	12%
Prasugrel	£18,866	£14,551	13.02	8.27	6.48	£133	0.03	£4,430	£115,058	1	84%	14%	2%	84%
Ticagrelor	£19,368	£15,089	12.88	8.18	6.41	£537	-0.07	Dominated	£113,140	3	2%	4%	94%	4%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
SA20: Discount rate 1.5%														
Clopidogrel	£19,358	£17,179	12.95	8.21	7.36				£129,960	2	13%	82%	5%	11%
Prasugrel	£19,511	£17,323	13.02	8.25	7.39	£144	0.04	£4,094	£130,520	1	85%	13%	2%	85%
Ticagrelor	£20,007	£17,838	12.87	8.16	7.31	£515	-0.08	Dominated	£128,386	3	2%	5%	93%	4%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Table 56: Sensitivity analyses results for scenario 3: STEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£23,149	£17,390	13.05	8.29	6.42				£111,065	3	0%	2%	98%	0%
Prasugrel	£23,842	£17,891	13.42	8.53	6.61	£501	0.18	£2,747	£114,213	1	95%	5%	0%	93%
Ticagrelor	£24,402	£18,471	13.31	8.45	6.55	£580	-0.06	Dominated	£112,442	2	5%	93%	2%	7%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£19,716	£14,990	13.08	8.36	6.47				£114,408	3	0%	1%	99%	0%
Prasugrel	£20,254	£15,385	13.46	8.60	6.66	£396	0.19	£2,131	£117,727	1	96%	4%	0%	93%
Ticagrelor	£20,810	£15,955	13.34	8.52	6.60	£570	-0.06	Dominated	£115,951	2	4%	95%	1%	7%
SA2: Rivaroxaban treatment effect included														
Prasugrel	£23,785	£17,851	13.43	8.53	6.61				£114,284	1	93%	6%	2%	89%
Ticagrelor	£24,337	£18,424	13.31	8.45	6.55	£573	-0.06	Dominated	£112,551	2	4%	59%	37%	6%
Clopidogrel	£24,392	£18,511	13.29	8.44	6.54	£87	-0.01	Dominated	£112,249	3	4%	36%	61%	5%
SA3: Utilities not age-adjusted														
Clopidogrel	£23,036	£17,307	13.05	10.76	8.27				£148,061	3	0%	1%	99%	0%
Prasugrel	£23,724	£17,805	13.42	11.07	8.50	£498	0.23	£2,124	£152,252	1	94%	6%	0%	92%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Ticagrelor	£24,284	£18,385	13.31	10.97	8.43	£580	-0.08	Dominated	£150,161	2	6%	93%	1%	8%
SA4: Dyspnoea included in analysis														
Clopidogrel	£23,106	£17,356	13.05	8.29	6.42				£111,135	3	0%	2%	98%	0%
Prasugrel	£23,797	£17,856	13.43	8.53	6.61	£499	0.18	£2,731	£114,292	1	96%	4%	0%	93%
Ticagrelor	£24,363	£18,442	13.31	8.45	6.55	£586	-0.06	Dominated	£112,519	2	4%	94%	2%	7%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£23,069	£17,335	13.05	8.29	6.42				£111,159	3	0%	2%	98%	0%
Prasugrel	£23,782	£17,854	13.43	8.53	6.61	£519	0.18	£2,846	£114,289	1	95%	5%	0%	92%
Ticagrelor	£24,331	£18,425	13.31	8.45	6.55	£570	-0.06	Dominated	£112,549	2	5%	93%	2%	8%
SA6: Major bleeding costs including intracranial bleeds (10%)														
Clopidogrel	£23,088	£17,346	13.05	8.29	6.42				£111,138	3	0%	2%	98%	0%
Prasugrel	£23,781	£17,848	13.42	8.53	6.61	£502	0.18	£2,762	£114,269	1	96%	4%	0%	93%
Ticagrelor	£24,343	£18,429	13.31	8.45	6.55	£581	-0.06	Dominated	£112,515	2	4%	94%	2%	7%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£23,079	£17,340	13.05	8.29	6.42				£111,156	3	0%	2%	98%	0%
Prasugrel	£23,773	£17,842	13.43	8.53	6.61	£502	0.18	£2,753	£114,299	1	95%	5%	0%	92%
Ticagrelor	£24,335	£18,423	13.31	8.45	6.55	£581	-0.06	Dominated	£112,545	2	5%	94%	2%	8%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£23,099	£17,355	13.05	8.29	6.42				£111,142	3	0%	2%	98%	0%
Prasugrel	£23,790	£17,855	13.43	8.53	6.61	£500	0.18	£2,735	£114,300	1	96%	4%	0%	93%
Ticagrelor	£24,351	£18,436	13.31	8.45	6.55	£581	-0.06	Dominated	£112,507	2	4%	94%	2%	7%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£23,024	£17,304	13.05	8.29	6.42				£111,158	3	0%	2%	98%	0%
Prasugrel	£23,717	£17,805	13.42	8.53	6.61	£501	0.18	£2,752	£114,300	1	95%	5%	0%	93%
Ticagrelor	£24,278	£18,387	13.31	8.45	6.55	£581	-0.06	Dominated	£112,547	2	5%	93%	2%	7%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£23,057	£17,328	13.05	8.29	6.42				£111,127	3	0%	2%	98%	0%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Prasugrel	£23,754	£17,835	13.42	8.53	6.60	£507	0.18	£2,808	£114,232	1	94%	5%	0%	92%
Ticagrelor	£24,315	£18,414	13.31	8.45	6.55	£579	-0.06	Dominated	£112,508	2	6%	93%	2%	8%
SA11: Percentage stroke social care costs publically funded - 30%														
Clopidogrel	£21,338	£16,163	13.05	8.29	6.42				£112,328	3	0%	2%	98%	0%
Prasugrel	£21,967	£16,624	13.43	8.53	6.61	£461	0.18	£2,514	£115,532	1	95%	5%	0%	92%
Ticagrelor	£22,485	£17,168	13.31	8.45	6.55	£545	-0.06	Dominated	£113,791	2	5%	93%	1%	8%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£24,896	£18,566	13.05	8.29	6.42				£109,899	3	0%	2%	98%	0%
Prasugrel	£25,659	£19,112	13.43	8.53	6.61	£545	0.18	£2,973	£113,023	1	96%	4%	0%	93%
Ticagrelor	£26,248	£19,717	13.31	8.45	6.55	£605	-0.06	Dominated	£111,196	2	4%	93%	2%	7%
SA13: Clopidogrel 300mg loading dose														
Clopidogrel	£23,091	£17,349	13.05	8.29	6.42				£111,127	3	0%	2%	98%	0%
Prasugrel	£23,789	£17,854	13.42	8.53	6.61	£505	0.18	£2,772	£114,264	1	95%	4%	0%	93%
Ticagrelor	£24,342	£18,428	13.31	8.45	6.55	£574	-0.06	Dominated	£112,507	2	5%	93%	2%	7%
SA14: Stroke treatment effect excluded														
Clopidogrel	£23,054	£17,324	13.05	8.29	6.42				£111,155	3	0%	1%	99%	0%
Prasugrel	£23,805	£17,871	13.42	8.53	6.60	£547	0.18	£3,043	£114,206	1	94%	6%	0%	91%
Ticagrelor	£24,143	£18,274	13.31	8.45	6.55	£403	-0.05	Dominated	£112,708	2	6%	93%	1%	9%
SA15: Ticagrelor's stroke treatment effect not included														
Clopidogrel	£23,128	£17,375	13.05	8.29	6.43				£111,142	3	0%	1%	99%	0%
Prasugrel	£23,823	£17,878	13.42	8.53	6.61	£503	0.18	£2,762	£114,280	1	94%	6%	0%	91%
Ticagrelor	£24,216	£18,325	13.31	8.46	6.55	£447	-0.06	Dominated	£112,691	2	6%	93%	1%	9%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£23,087	£17,345	13.05	8.29	6.42				£111,119	3	0%	2%	98%	0%
Prasugrel	£23,837	£17,892	13.43	8.53	6.60	£547	0.18	£3,026	£114,188	1	95%	5%	0%	92%
Ticagrelor	£24,338	£18,425	13.31	8.45	6.55	£533	-0.06	Dominated	£112,504	2	5%	93%	2%	8%
SA18: Reduce SMR for ACS/Reinfarction by 20%														

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Clopidogrel	£24,715	£18,282	14.18	8.97	6.83				£118,240	3	0%	2%	98%	0%
Prasugrel	£25,457	£18,812	14.59	9.23	7.02	£530	0.19	£2,743	£121,573	1	95%	5%	0%	93%
Ticagrelor	£25,993	£19,377	14.46	9.14	6.96	£565	-0.06	Dominated	£119,732	2	5%	94%	2%	7%
SA19: Include baseline risk adjustment														
Clopidogrel	£21,845	£16,416	13.17	8.38	6.48				£113,182	3	0%	2%	98%	0%
Prasugrel	£22,477	£16,877	13.54	8.62	6.66	£462	0.18	£2,525	£116,378	1	95%	5%	0%	93%
Ticagrelor	£23,035	£17,451	13.42	8.54	6.60	£573	-0.06	Dominated	£114,622	2	5%	93%	2%	7%
SA20: Discount rate 1.5%														
Clopidogrel	£23,064	£20,262	13.05	8.29	7.39				£127,452	3	0%	1%	99%	0%
Prasugrel	£23,755	£20,858	13.42	8.53	7.60	£597	0.21	£2,829	£131,072	1	95%	5%	0%	92%
Ticagrelor	£24,318	£21,431	13.31	8.45	7.53	£573	-0.07	Dominated	£129,143	2	5%	94%	1%	8%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

Table 57: Sensitivity analyses results for scenario 3: UA/NSTEMI population (probabilistic analysis, per person results)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Basecase results														
Clopidogrel	£19,396	£14,898	12.95	8.21	6.44				£113,902	3	0%	2%	99%	0%
Prasugrel	£19,791	£15,199	13.21	8.37	6.56	£301	0.12	£2,452	£116,054	1	99%	1%	0%	98%
Ticagrelor	£20,342	£15,768	13.11	8.31	6.52	£569	-0.05	Dominated	£114,539	2	1%	98%	1%	2%
SA1: Stroke baseline risks adjusted based on PLATO														
Clopidogrel	£16,974	£13,186	12.98	8.26	6.47				£116,300	3	0%	1%	100%	0%
Prasugrel	£17,300	£13,439	13.23	8.43	6.60	£253	0.12	£2,033	£118,538	1	99%	1%	0%	98%
Ticagrelor	£17,840	£13,997	13.14	8.36	6.55	£558	-0.05	Dominated	£117,027	2	1%	99%	0%	2%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
SA2: Rivaroxaban treatment effect included														
Prasugrel	£19,737	£15,161	13.21	8.37	6.56				£116,100	1	99%	1%	0%	97%
Ticagrelor	£20,282	£15,726	13.11	8.31	6.52	£565	-0.05	Dominated	£114,606	2	1%	74%	25%	2%
Clopidogrel	£20,318	£15,778	13.08	8.29	6.50	£52	-0.01	Dominated	£114,267	3	0%	25%	75%	1%
SA3: Utilities not age-adjusted														
Clopidogrel	£19,299	£14,827	12.95	10.76	8.37				£152,596	3	0%	0%	100%	0%
Prasugrel	£19,692	£15,127	13.20	10.97	8.53	£299	0.16	£1,878	£155,485	1	98%	2%	0%	98%
Ticagrelor	£20,243	£15,697	13.11	10.89	8.47	£570	-0.06	Dominated	£153,702	2	2%	98%	0%	2%
SA4: Dyspnoea included in analysis														
Clopidogrel	£19,360	£14,872	12.95	8.21	6.44				£113,930	3	0%	2%	98%	0%
Prasugrel	£19,755	£15,172	13.21	8.37	6.56	£300	0.12	£2,438	£116,091	1	99%	1%	0%	99%
Ticagrelor	£20,310	£15,746	13.11	8.31	6.52	£574	-0.05	Dominated	£114,570	2	1%	98%	2%	1%
SA5: Minor bleeding costs set to GI bleed														
Clopidogrel	£19,324	£14,847	12.95	8.21	6.44				£113,963	3	0%	2%	98%	0%
Prasugrel	£19,730	£15,158	13.20	8.37	6.56	£311	0.12	£2,537	£116,105	1	99%	1%	0%	98%
Ticagrelor	£20,274	£15,722	13.11	8.31	6.52	£563	-0.05	Dominated	£114,604	2	1%	97%	2%	2%
SA6: Major bleeding costs including intracranial bleeds (10%)														
Clopidogrel	£19,340	£14,857	12.96	8.21	6.44				£113,964	3	0%	1%	99%	0%
Prasugrel	£19,735	£15,158	13.21	8.37	6.56	£301	0.12	£2,469	£116,103	1	99%	1%	0%	98%
Ticagrelor	£20,287	£15,728	13.11	8.31	6.52	£570	-0.05	Dominated	£114,602	2	1%	98%	1%	2%
SA7: Major bleeding costs including intracranial bleeds (20%)														
Clopidogrel	£19,333	£14,854	12.95	8.21	6.44				£113,955	3	0%	1%	99%	0%
Prasugrel	£19,729	£15,155	13.20	8.37	6.56	£301	0.12	£2,459	£116,105	1	99%	1%	0%	98%
Ticagrelor	£20,280	£15,725	13.11	8.31	6.52	£570	-0.05	Dominated	£114,597	2	1%	98%	1%	2%
SA8: Intracranial bleeds set to 30% of major bleeds														
Clopidogrel	£19,347	£14,864	12.95	8.21	6.44				£113,943	3	0%	2%	99%	0%
Prasugrel	£19,741	£15,165	13.21	8.37	6.56	£300	0.12	£2,443	£116,102	1	99%	1%	0%	98%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Ticagrelor	£20,293	£15,735	13.11	8.31	6.52	£571	-0.05	Dominated	£114,578	2	1%	98%	2%	2%
SA9: Intracranial bleeds set to 40% of major bleeds														
Clopidogrel	£19,282	£14,819	12.95	8.21	6.44				£113,979	3	0%	2%	98%	0%
Prasugrel	£19,677	£15,119	13.20	8.37	6.56	£301	0.12	£2,463	£116,119	1	99%	1%	0%	98%
Ticagrelor	£20,229	£15,690	13.11	8.31	6.52	£570	-0.05	Dominated	£114,621	2	1%	97%	2%	2%
SA10: Higher minor and major bleeding costs (intracranial 20%)														
Clopidogrel	£19,309	£14,839	12.95	8.21	6.44				£113,942	3	0%	1%	99%	0%
Prasugrel	£19,708	£15,144	13.20	8.37	6.56	£305	0.12	£2,502	£116,075	1	99%	1%	0%	98%
Ticagrelor	£20,258	£15,712	13.11	8.31	6.51	£568	-0.05	Dominated	£114,581	2	1%	98%	1%	2%
SA11: Percentage stroke social care costs publically funded - 30%														
Clopidogrel	£18,437	£14,240	12.95	8.21	6.44				£114,575	3	0%	1%	99%	0%
Prasugrel	£18,810	£14,527	13.21	8.37	6.56	£287	0.12	£2,335	£116,744	1	99%	1%	0%	98%
Ticagrelor	£19,343	£15,081	13.11	8.31	6.52	£555	-0.05	Dominated	£115,247	2	1%	98%	1%	2%
SA12: Percentage stroke social care costs publically funded - 70%														
Clopidogrel	£20,282	£15,500	12.95	8.21	6.44				£113,304	3	0%	2%	98%	0%
Prasugrel	£20,700	£15,816	13.21	8.37	6.56	£315	0.12	£2,559	£115,453	1	99%	1%	0%	98%
Ticagrelor	£21,265	£16,397	13.11	8.31	6.52	£582	-0.05	Dominated	£113,915	2	1%	97%	2%	2%
SA13: Clopidogrel 300mg loading dose														
Clopidogrel	£19,342	£14,859	12.95	8.21	6.44				£113,950	3	0%	1%	99%	0%
Prasugrel	£19,740	£15,162	13.21	8.37	6.56	£303	0.12	£2,471	£116,100	1	99%	1%	0%	98%
Ticagrelor	£20,287	£15,728	13.11	8.31	6.52	£567	-0.05	Dominated	£114,594	2	1%	98%	1%	2%
SA14: Stroke treatment effect excluded														
Clopidogrel	£19,314	£14,840	12.95	8.21	6.44				£113,972	3	0%	1%	99%	0%
Prasugrel	£19,734	£15,162	13.20	8.37	6.56	£322	0.12	£2,650	£116,077	1	99%	1%	0%	98%
Ticagrelor	£20,184	£15,650	13.11	8.31	6.52	£488	-0.04	Dominated	£114,690	2	1%	98%	1%	2%
SA15: Ticagrelor's stroke treatment effect not included														
Clopidogrel	£19,378	£14,886	12.95	8.21	6.44				£113,957	3	0%	1%	99%	0%

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)	Rank at £20k	% CE at £20k	% Rank 2nd (£20k)	% Rank 3rd (£20k)	% CE at £30k
Prasugrel	£19,775	£15,188	13.21	8.37	6.56	£302	0.12	£2,467	£116,104	1	99%	1%	0%	98%
Ticagrelor	£20,248	£15,695	13.11	8.31	6.52	£507	-0.05	Dominated	£114,678	2	1%	98%	0%	2%
SA16: Prasugrel's stroke treatment effect not included														
Clopidogrel	£19,353	£14,868	12.95	8.21	6.44				£113,926	3	0%	1%	99%	0%
Prasugrel	£19,773	£15,188	13.20	8.37	6.56	£321	0.12	£2,631	£116,043	1	99%	1%	0%	98%
Ticagrelor	£20,299	£15,738	13.11	8.31	6.52	£550	-0.05	Dominated	£114,571	2	1%	98%	1%	2%
SA17: UA/NSTEMI prasugrel arm receiving clopiodgrel loading dose														
Clopidogrel	£19,397	£14,900	12.95	8.21	6.44				£113,902	3	0%	1%	99%	0%
Prasugrel	£19,793	£15,201	13.21	8.37	6.56	£301	0.12	£2,458	£116,053	1	99%	1%	0%	98%
Ticagrelor	£20,342	£15,770	13.11	8.31	6.52	£569	-0.05	Dominated	£114,548	2	1%	98%	1%	2%
SA18: Reduce SMR for ACS/Reinfarction by 20%														
Clopidogrel	£20,906	£15,782	14.14	8.92	6.87				£121,639	3	0%	1%	99%	0%
Prasugrel	£21,329	£16,098	14.42	9.10	7.00	£317	0.13	£2,432	£123,927	1	99%	1%	0%	98%
Ticagrelor	£21,866	£16,660	14.31	9.03	6.95	£561	-0.05	Dominated	£122,358	2	1%	98%	1%	2%
SA19: Include baseline risk adjustment														
Clopidogrel	£18,674	£14,386	12.96	8.22	6.45				£114,578	3	0%	1%	99%	0%
Prasugrel	£19,049	£14,673	13.21	8.39	6.57	£287	0.12	£2,334	£116,752	1	99%	1%	0%	98%
Ticagrelor	£19,596	£15,239	13.12	8.32	6.52	£566	-0.05	Dominated	£115,239	2	1%	98%	1%	2%
SA20: Discount rate 1.5%														
Clopidogrel	£19,330	£17,156	12.95	8.21	7.36				£130,013	3	0%	1%	99%	0%
Prasugrel	£19,725	£17,505	13.20	8.37	7.50	£349	0.14	£2,465	£132,497	1	99%	1%	0%	98%
Ticagrelor	£20,278	£18,067	13.11	8.31	7.45	£561	-0.05	Dominated	£130,856	2	1%	98%	1%	2%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years
** at a threshold of £20,000 per QALY gained*
*** at a threshold of £30,000 per QALY gained*

4 Discussion

4.1 Summary of results

Due to inconsistency in the 1-year clinical treatment effect data, three scenarios using different sets of clinical data were undertaken in the cost effectiveness analysis. The three scenarios utilise the following data to inform the relative treatment effects between 31 days and 1 year in the model (all scenarios use the 30 day NMA to inform the relative treatment effects 0 to 30 days in the model):

1. Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)
2. Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)
3. Ticagrelor vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)

Prasugrel was the most cost effective DAPT option in all data scenarios and ACS subgroups except in a UA/NSTEMI population when data from studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel (and not ISAR-REACT 5) was used to inform the relative treatment effects between 31 days and 1 year in the model (data scenario 1). This scenario resulted in ticagrelor being cost effective for UA/NSTEMI.

Ticagrelor had the highest costs in all scenarios and ACS subgroups but only had the highest QALYs in scenario 1. In scenarios 2 and 3 prasugrel had lower costs than ticagrelor and higher QALYs. Clopidogrel had the lowest costs in all scenarios however there was little uncertainty that clopidogrel was not the most cost effective option.

Although prasugrel was overall the most cost effective option in a STEMI population, when data from studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel was used to inform the relative treatment effects between 31 days and 1 year in the model (data scenario 1), there was a lot of uncertainty between whether prasugrel or ticagrelor was the most cost effective option with prasugrel only being the most cost effective option in 53% of simulations, and ticagrelor being the most cost effective in 47% of simulations. In addition, ticagrelor became the most cost-effective option in a number of sensitivity analyses, highlighting the uncertainty between whether prasugrel or ticagrelor was the most cost effective option in this scenario. There was less uncertainty in scenario 1 in the UA/NSTEMI analysis with ticagrelor being cost effective in 63% of simulations and prasugrel being cost effective in 37% of simulations.. The conclusion that ticagrelor was the most cost effective option for UA/NSTEMI in this data scenario was robust to a wide range of sensitivity analyses.

However, there was little uncertainty that prasugrel was the most cost-effective option in data scenarios 2 and 3 that utilise the recent ISAR-REACT 5 RCT comparing prasugrel and ticagrelor to inform the relative treatment effects between 31 days and 1 year in the model with high probabilities of cost effectiveness for both STEMI and NSTEMI. This conclusion was also robust to a wide range of sensitivity analyses around costs, stroke treatment effects, baseline risks and mortality.

When the use of rivaroxaban was incorporated into the clopidogrel group results were impacted as clopidogrel had the highest costs and QALYs increased, however conclusions on which treatment option was the most cost effective remained unchanged..

4.2 Limitations and interpretation

Baseline risks in 1 year decision tree

In the model we aimed to use baseline risks based on UK audit data in order to reflect real world risks for people with ACS. As discussed in the methods, the ideal source of baseline

risks for the model would have been to undertake a bespoke analysis of national audit data linked with mortality and HES data as this would allow calculation of probabilities that matched the decision tree exactly, for example the probability of reinfarction 31 days to 1 year given you did or did not have an event 0 to 30 days, but this was not feasible within guideline development time constraints. Published audit data analyses were therefore used in the model and probabilities 31 days to 1 year were assumed to be independent of events experienced 0 to 30 days.

As the baseline risks were to populate the clopidogrel arm, it was ideal that the data was obtained from people in England who underwent PCI and were taking clopidogrel. One of the limitations was that the data for baseline risks was not solely people taking clopidogrel. For example, the mortality data was taken from BCIS audit from 2011/12 and clopidogrel use was 77.8% for STEMI and 98.5% for UA/NSTEMI. The use of clopidogrel in the UA/NSTEMI population was very high, but the use was lower for STEMI. Although this was a limitation, the committee agreed that this was reasonable. Firstly, it was noted that people taking clopidogrel in more recent audit data may not be a good representation of the average population, for example, they have a higher bleeding risk due to age. Therefore, the committee agreed using the data from 2011/12 was a good balance between having a majority of people on clopidogrel and being relevant to current practice.

As described in section 2.3.2.1, the baseline risk data for stroke (in both STEMI and UA/NSTEMI) and reinfarction (only in STEMI) was for all events instead of non-fatal events. This may overestimate the number of people that are alive with an event at the end of the decision tree and entering the Markov model. This has implications as the health states for post-reinfarction and post-stroke result in higher costs and lower quality of life. In order to address this a sensitivity analysis was undertaken using lower probabilities for these events and this did not impact conclusions.

The committee noted that the mortality rates for UA/NSTEMI appeared lower than might be expected. However, it was agreed that this was due to the fact this analysis only included the PCI population, and it is those who are medically managed that might have a higher mortality rate. This was reinforced by the analysis of audit data undertaken in CG94 which showed that people that underwent PCI had a lower mortality rate. Also, the most recent BCIS audit report for 2017/18 showed that the 30-day mortality rate was 1.6% for people with UA/NSTEMI that underwent PCI which is very similar to the 1.79% used in the model.

Another limitation was that there was no recent data for reinfarction for the UA/NSTEMI population, and therefore the previous MINAP analysis that was conducted for the UA/NSTEMI NICE Guideline CG94 was used. This is based on data from 2005 to 2007 and may not be as reflective of current practice. However, everyone in the analysis would have been taking clopidogrel and therefore the committee felt this was a reasonable source to use. Also, the analysis only reported reinfarction at 1 year, and an assumption had to be made about the reinfarction rate at 30 days. In order to obtain this rate, the relationship between 31 days and 1 year reinfarction rates from a Swedeheart analysis and the PLATO trial was obtained. These showed a similar relationship and the committee agreed this was a reasonable way to obtain the 30 day reinfarction rate.

The source of baseline risk for stroke did not report 1-year event rates for either STEMI or UA/NSTEMI. Therefore, a similar approach had to be taken to obtain the relationship between 31 day and 1 year event rates. The relationship observed in the Swedeheart audit and PLATO trial were both discussed but as they were quite different, the committee agreed to use the relationship from the Swedeheart audit in the base case and to test using the data from the PLATO trial in a sensitivity analysis; and this did not impact conclusions.

There was no data available for minor and major bleeds from a UK audit. As a result, data from the PLATO RCT was used as it was considered the trial that was closest to UK practice. One limitation was that the PLATO trial included CABG related bleeding in their major and minor bleeding outcomes, and did not report non-CABG related bleeding for minor bleeds.

As a result, assumptions had to be made about the relationships between major and minor bleeds, as well as the relationship between 31 day and 1 year bleeding events. The committee acknowledged this was a limitation, however, considered this to be the best available estimate.

Treatment effects

The treatment effects used in the model were obtained from the network meta-analysis (30 day data) and pairwise meta-analyses undertaken as part of guideline development (see Evidence report A and NMA report).

The RCTs that informed treatment effects varied in terms of their ACS population with some conducted in the overall ACS population and some in a particular ACS subtype (STEMI or UA/NSTEMI). They also varied in terms of management strategy with some only including people receiving PCI and others including all management strategies. It was considered appropriate by the committee to assume that relative treatment effects were consistent and that combining ACS data together provided the best estimate of treatment effects. This may have limitations as it can be said that STEMI and UA/NSTEMI differ clinically, for example, STEMI is a medical emergency requiring urgent treatment. Although they may differ with regards to some clinical aspects, the committee reviewed the clinical evidence stratified by subtype (STEMI or UA/NSTEMI) and also by management approach (PCI or medically managed) and agreed that treatment effects were sufficiently consistent. It was therefore deemed appropriate to combine these to get the best estimate of treatment effects. This approach has been undertaken by other clinical reviews and in randomised controlled trials, for example the PLATO trial assessed the overall ACS population.

The NMA of 30-day outcomes included 14 RCTs; however, there were some limitations of the RCTs included. Firstly, the TRITON-TIMI 38 trial did not report 30 day outcomes for the overall ACS population and only reported 30 day outcomes for the STEMI population. This trial was the largest RCT comparing prasugrel and clopidogrel in over 13,000 patients, but the sub-analysis of the STEMI population only included over 3,000 patients. The committee considered this study significant for the comparison of prasugrel versus clopidogrel; therefore the absence of a large number of participants was considered a limitation of the NMA. Another RCT that was not included in the NMA as 30 day data was not available and was considered a significant study was the ISAR-REACT 5 trial. This study was conducted in over 3,000 participants and was considered a very important trial comparing ticagrelor and prasugrel. The studies included in the NMA for the ticagrelor vs prasugrel comparison were conducted on a small number of participants in comparison to the ISAR-REACT 5; therefore not including this study was considered a limitation of the 30 day outcome data from the NMA. Note however that both ISAR-REACT 5 and the full TRITON-TIMI 38 population data are incorporated into the model as part of the 1 year relative treatment effects.

Another limitation was studies used to inform relative treatment effects did not always report both 30 day and 1 year treatment effects, resulting in different studies contributing to the 30 day and 1 year relative treatment effects used in the model. The committee considered the data available at 1 year to be the most complete however it was not possible to obtain a single set of consistent treatment effects incorporating all available data at 1 year due to the there being a high level of inconsistency across the ‘direct’ and ‘indirect’ estimates of effect in the evidence network which meant NMA was considered unreliable. As a result, the economic analysis had to utilise data from two sides of the network at one given time, resulting in 3 alternative base case scenarios, in order to explore the impact of the inconsistency in the clinical evidence on cost effectiveness conclusions. From the clinical and cost effectiveness evidence it was evident that clopidogrel was not the most clinically and cost-effective option. When ticagrelor and prasugrel were compared to clopidogrel individually they were the most effective and cost-effective options. However, when assessing all comparators, the alternative base case scenarios resulted in different

conclusions; the inconsistency in the data was therefore an important issue to consider when interpreting the results.

The relative treatment effects that were applied in the 31 days to 1 year part of the decision tree were taken from the 1 year outcome pairwise meta-analyses. It would have been ideal to remove the events that occurred up to 30 days from the 1 year data; however, most of the studies with results at 1 year did not report 30 day data, or the available 30 day data was not for the same population. This was discussed and it was agreed that the direction of treatment effects were unlikely to change between 30 days and 1 year and therefore using the 1 year relative treatment effects was a reasonable approach for the purpose of modelling. This was applied to baseline risks specifically for 31 days to 1 year.

The sensitivity analysis conducted which included rivaroxaban in the clopidogrel arm showed that conclusions about the most cost-effective option were not changed. As rivaroxaban is only indicated alongside clopidogrel, a recommendation for one of the other antiplatelets would preclude rivaroxaban's use, therefore an exploratory analysis was undertaken where treatment effects of rivaroxaban were incorporated into the model to see if this would impact results. However, there were limitations associated with this analysis. The treatment effects reported in the ATLAS-TIMI trial were hazard ratios at 24 months. As treatment effects were not reported at the specific time points of interest (30 days and 1 year) it was assumed that treatment effects remained constant. The committee agreed this was a reasonable approach for this exploratory sensitivity analysis. The available data also relates a longer time point than was considered in this analysis, however, the study showed that on average rivaroxaban was taken for 13 months, therefore applying these at 1 year was considered reasonable. The committee noted that only a small number of people are prescribed low dose rivaroxaban and clopidogrel after ACS currently.

There was uncertainty around including the treatment effects of stroke in the model as it was unclear if there were differences between treatments and because stroke affects a small number of people. There was some uncertainty in the treatment effect estimates as some trials reported no events or only a very small number of events. It was acknowledged that stroke events have high costs associated with them and therefore a small number of events could impact costs considerably and also have a large impact on QALYs. However, this was tested in a sensitivity analysis by removing the treatment effects of stroke from the analysis to see if this impacted results. This only impacted conclusions in scenario 1 for STEMI, which resulted in ticagrelor becoming the most cost effective option. This emphasised that there was a lot of uncertainty between whether prasugrel or ticagrelor was the most cost effective option in this scenario for STEMI.

Events beyond one year

Data was not identified about risks of stroke or reinfarction in an ACS population beyond one year and so it was assumed that the rate beyond one year would be the same as that between 31 days and 1 year. It can be considered a limitation that there was no real world data available for the rate of reinfarction or stroke beyond one year to inform this decision. However, this is an approach that was used in other ACS models and the committee agreed it was a reasonable assumption.

The model did not allow for repeat events after 1 year and only allowed people in the no further event health state to have a reinfarction or stroke, and if they had one event they could not have the other event too. This can be considered a limitation as this does not reflect the real world as people can experience repeat reinfarctions and stroke. However, this was considered to be a reasonable simplification for modelling purposes as there is limited data available to model repeat events beyond one year and would require making too many assumptions. In addition, this was taken into account when selecting health state cost data where costs incorporating downstream events were used if possible.

It was considered that the mortality transition probabilities could be over or underestimating death in the model. The study used to obtain the SMRs for the no further event, reinfarction and post-reinfarction health states was for people with a myocardial infarction, and not just PCI. It was thought that this could potentially overestimate the mortality rates. Also, the study analysed mortality for people who have had their first myocardial infarction separately to those with a second myocardial infarction. The data for those that had their first myocardial infarction was used for the no further event health state in the model, however, some of these people being modelled would have had a previous myocardial infarction, therefore this could be underestimating mortality for this group. It was considered that despite these limitations, this was a good source of data and being able to utilise different SMRs for the no further event and reinfarction/post-reinfarction health states was important. Lastly, it was discussed that the SMRs from the study would include death from any cause, therefore this would include people who are dying from having a stroke. As a result, this could overestimate the number of people dying in each cycle, as the ACS SMRs have not been adjusted to account for the fact that people with a stroke is being captured separately. A sensitivity analysis was conducted where the SMRs for the ACS health states (no further event, reinfarction and post-reinfarction) were reduced by 20% and this did not impact conclusions. In order to further test whether mortality in the model was accurate, the 5-year survival rate for STEMI was calculated and compared to the reported 5 year survival rate in a study by Brogan 2017[4] for people with STEMI that underwent PCI. Results were similar, with the study reporting that 87% of people survive 5 years and the model showing that 85% survived 5 years.

Costs

There were some assumptions made in relation to the costs. Firstly, the costs associated with ACS and applied to everyone were obtained from a study which reported the cost of myocardial infarction for people who were receiving lipid modifying therapy. Although this is not the exact population being modelled, the committee agreed that whether you are taking lipid modifying treatment before an event should not impact the treatment you receive for having a myocardial infarction, and therefore the costs should not be impacted. These costs were applied to both the STEMI and UA/NSTEMI population. It was noted that as unstable angina is not classified as a myocardial infarction, this could be overestimating the costs associated with these people. However, the committee agreed that as the model looked at people undergoing PCI, the downstream management and resource use would be similar to those with myocardial infarction and therefore this was considered a reasonable approach.

The costs associated with stroke were obtained from SSNAP data, which was considered the most reliable source of UK stroke data. However, some assumptions were made around the social care costs. As the SSNAP costs included both publically and non-publically funded social care costs, these had to be adjusted to ensure only the costs incurred to the NHS and personal social services were included. The percentage that was publically funded was not reported; therefore an assumption had to be made. The committee agreed it was reasonable to follow the assumption made in an analysis by the Stroke Association which indicated that 50% of social care costs were publically funded. This was also explored in a sensitivity analysis where 30% and 70% of these costs were assumed to be publically funded, and this did not impact conclusions.

The costs of major and minor bleeding were based on what the committee considered were relevant NHS reference costs. For minor bleeds, the cost of an emergency admission was used. Although it was noted that minor bleeds may not require medical interventions, it was discussed that people experiencing a minor bleed may feel anxious as they have just had an ACS event, and therefore seek medical help. The costs associated with an emergency admission were used in a previous NICE technology appraisal, and the committee considered this a reasonable cost. There was variation in what other models in the areas had used to cost minor bleeds, and as a result a sensitivity analysis was conducted which costed a gastrointestinal bleed without interventions, and this did not impact conclusions. Major

bleeds were costed as gastrointestinal bleeds with interventions, and gastrointestinal bleeds without interventions with a high comorbidity score (5+). It was discussed that major bleeding can also include intracranial bleeds; however, gastrointestinal bleeds were more common in this population. Sensitivity analyses were conducted which included intracranial bleeds in the costs of a major bleed, and these did not impact conclusions.

4.3 Generalisability to other populations or settings

The relative treatment effects used in the model were for the overall ACS population and therefore included people who were not invasively managed. Also, the same treatment effects were applied to the STEMI and UA/NSTEMI populations. The committee considered the pairwise meta-analyses stratified by condition and management approach, as well as the evidence for all ACS, and considered it was reasonable to assume that relative treatment effects were consistent and combining all the evidence provided the best estimate of treatment effects. To account for the fact that event rates may differ by subgroup, different baseline risks were used for the STEMI and UA/NSTEMI populations, and therefore absolute event rates were different.

The committee acknowledged that the people recruited to randomised controlled trials are generally younger and/or lower risk than the overall ACS population. However, this was partially addressed in the model by using baseline risks associated with real world ACS PCI population in order to estimate real world absolute event rates with the different treatment options. Although noting these issues, the committee agreed that it was appropriate to use the available clinical effectiveness and cost effectiveness evidence to make recommendations for the whole ACS PCI population,

4.4 Comparisons with published studies

The economic literature review results are detailed in full in Evidence report A. Five published economic evaluations were included in the review. Two compared ticagrelor, prasugrel and clopidogrel, two compared ticagrelor and clopidogrel, one compared prasugrel and clopidogrel and one compared ticagrelor and prasugrel. One of the analyses that compared ticagrelor and clopidogrel is not relevant to this analysis as it looked at people with ACS that were medically managed, therefore, this is not included in this discussion.

One published economic evaluation (NICE TA236)[38] compared ticagrelor with clopidogrel in the overall ACS population (invasive and non-invasive management) using a probabilistic decision analytic model. The new analysis for the guideline takes a similar approach as it was conducted from a UK NHS and personal social services perspective and used a decision tree to model first year events and a Markov model for long term extrapolation, with the same health states. The analysis found that ticagrelor had higher costs and QALYs and was cost effective with an ICER of £3,805 per QALY gained. These results are consistent with the results in this analysis if excluding prasugrel. When prasugrel is not included, ticagrelor is cost effective in comparison to clopidogrel in scenarios 1 and 3 (but not in scenario 2). The QALY gain between ticagrelor and clopidogrel is similar in this analysis for scenarios 1 and 3 compared to the NICE TA, however, the incremental costs are slightly higher. It is likely this is due to the costs used in the current analysis being higher than the costs used in NICE TA236. For example, the Markov model costs for the no further event health state was £217 compared to £943 in the new analysis. The reinfarction health sate cost was similar however the post-reinfarction health state cost was £1,415 in the new analysis but only £285 in NICE TA236. The post-stroke health sate had a similar cost, however, the stroke health state costs in NICE TA236 was £13,084 compared to £18,522 in the new analysis. As more people were alive in the ticagrelor arm in scenarios 1 and 2, this means that more costs would have been accrued over time. Due to higher costs being used and more people being alive in the ticagrelor arm, this would have contributed to the higher difference in incremental costs and result in higher incremental cost effectiveness ratios. The

same study also conducted an analysis comparing ticagrelor and prasugrel, however, this was based on an indirect comparison of ticagrelor versus prasugrel as there were no published trials at the time that had compared ticagrelor and prasugrel. The results from that analysis differ considerably from the results in the new analysis, as they showed that ticagrelor was cost effective compared to prasugrel, with an ICER of £3,482 per QALY gained. The current analysis undertaken for this guideline showed that ticagrelor was dominated by prasugrel in scenario 2 and 3, and that ticagrelor was cost effective compared to prasugrel for UA/NSTEMI in scenario 1 but not for STEMI. The results are similar for scenario 1 in UA/NSTEMI but differ considerably to scenarios 2 and 3 and this is due to the fact an indirect treatment comparison was used as there was no head to head data for prasugrel and ticagrelor. The analysis for this guideline utilised new head to head data for prasugrel and ticagrelor which showed that prasugrel was more effective in comparison to ticagrelor.

Greenhalgh 2015[14] conducted an economic evaluation of prasugrel versus clopidogrel in people with ACS undergoing PCI and was the evidence review group report for NICE TA317. This analysis split the ACS population in to four subgroups which included STEMI with and without diabetes and UA/NSTEMI with and without diabetes. Prasugrel was found to be cost-effective in comparison to clopidogrel, with an ICER of £6,687 per QALY gained for people with STEMI and without diabetes, £1,643 for people with STEMI and diabetes, £4,679 for people with UA/NSTEMI without diabetes and was dominant (higher QALYs and lower costs compared to clopidogrel) for the UA/NSTEMI group with diabetes. One difference between this analysis and the new analysis is the cost of prasugrel. The NICE TA317 used a pack price of £47.56 and this cost has significantly decreased. This analysis reported higher lifetime costs across all subgroups in comparison to the new analysis. A breakdown of the costs showed that the no further event and reinfarction health state costs were similar, however, the costs associated with stroke over the lifetime were higher in this analysis compared to the new analysis. This may be due to the analysis separating stroke in to disabling and non-disabling stroke, and having a higher cost associated with disabling stroke over a long period of time. Another contributing factor could be the fact that the start age in the analysis was lower and therefore people were alive for a longer period of time and therefore accruing more costs. Despite the higher lifetime costs, incremental costs were similar, apart from the UA/NSTEMI with diabetes group, where prasugrel resulted in less costs. The lifetime QALYs were also higher across all subgroups in this analysis compared to the new analysis. This could be due to the new analysis for the guideline having a higher start age and therefore having a lower life expectancy, which would accrue less QALYs. Also, Greenhalgh 2015 did not apply a lower quality of life to those who had a second myocardial infarction, and this could further explain the differences in the lifetime QALY estimates.

Two economic evaluations conducted a three-way analysis of ticagrelor, prasugrel and clopidogrel. Abdel-Qadir 2015[1] conducted an analysis from a Canadian healthcare perspective and found that ticagrelor had the highest costs and QALYs followed by prasugrel and then clopidogrel. Prasugrel was extendedly dominated by ticagrelor and the ICER for ticagrelor versus clopidogrel was £6,556 per QALY gained. This analysis was based on data collected in three randomised controlled trials, two of which compared ticagrelor and clopidogrel (DISPERSE-2 and PLATO) and one which compared prasugrel to clopidogrel (TRITON-TIMI 38). Therefore, this analysis did not include head-to-head data for ticagrelor versus prasugrel. The analysis reported higher lifetime QALYs compared to the new analysis, and this is due to the utility values being much higher than the values used in the new analysis. For example, the no further event health state utility value was 0.91 compared to 0.84. Also, the analysis did not indicate whether quality of life was age-adjusted, and this could contribute to the analysis having higher QALYs. The sensitivity analysis conducted in the new analysis for the guideline where utilities were not age-adjusted also resulted in higher QALYs. The lifetime costs were also higher and the incremental cost between ticagrelor and prasugrel was lower. Wisloff 2015[56] was the second three-way analysis which was conducted from a Norwegian healthcare perspective. This analysis found that ticagrelor

had the highest costs and QALYs followed by prasugrel and then clopidogrel. The ICER for prasugrel versus clopidogrel was £6,107 per QALY gained and the ICER for ticagrelor versus prasugrel was £6,210 per QALY gained and ticagrelor was considered the most cost-effective option. The lifetime QALYs were higher in this analysis compared to the new analysis, however the paper did not give details of what utility values were used. The difference in lifetime costs between the treatments was much bigger than the incremental costs in the new analysis, but due to the absence of detail regarding costs in the study, it is unclear why. The results from these three-way analyses are very different to the new analysis undertaken as part of guideline development, especially scenarios two and three. The main reason for these differences is because they did not have head-to-head data for ticagrelor and prasugrel, and the new head-to-head data shows that prasugrel is more effective than ticagrelor, which resulted in the new analysis having higher QALYs associated with prasugrel.

4.5 Conclusions

This analysis found that the DAPT option that was most cost effective depended on the clinical data used to inform relative treatment effects between 31 days and 1 year. Ticagrelor (plus aspirin) was the most cost effective option for UA/NSTEMI in data scenario 1 which used data from studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel (and not ISAR-REACT 5). Prasugrel was the most cost effective option for STEMI in the same data scenario, although there was considerable uncertainty between prasugrel and ticagrelor. Prasugrel (plus aspirin) was the most cost effective option in data scenarios 2 and 3, which utilised data from ISAR-REACT 5.

4.6 Implications for future research

There have been various economic evaluations looking at the cost effectiveness of dual-antiplatelet therapy. This is the first UK analysis which has included the results from the ISAR-REACT 5 trial, which is the first large randomised controlled trial comparing ticagrelor and prasugrel. Due to the uncertainty around the applicability of the ISAR-REACT 5 trial to a UA/NSTEMI population in the UK, it would be beneficial to conduct a UK study in this population undergoing PCI, comparing ticagrelor and prasugrel.

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